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Studies on Sulfadiazine. I. The Chemotherapy of Experimental Haemolytic Streptococcal, Pneumococcal and Staphylococcal Infections in Mice. PERRIN H. LONG, M.D., ELEANOR A. BLISS, SC.D., AND EARL OTT..... 297

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STUDIES ON SULFADIAZINE

I. The Chemotherapy of Experimental Haemolytic Streptococcal, Pneumococcal and Staphylococcal Infections in Mice[1]

PERRIN H. LONG, M.D., ELEANOR A. BLISS,[2] Sc.D., and EARL OTT

From the Department of Preventive Medicine, The Johns Hopkins University

Submitted for publication July 7, 1941

Roblin and his associates (1) have described the preparation of certain heterocyclic sulfonamide compounds. Among them were 2-sulfanilamidopyrimidine, 2 N^4-acetylsulfanilamidopyrimidine, 2-sulfanilamido - 4 - methylpyrimidine, 2 - N^4 - acetylsulfanilamido - 4 - methylpyrimidine, and 4-sulfanilamidopyrimidine. One of these compounds, 2-sulfanilamidopyrimidine, to which the name of *sulfadiazine* has been given in order to prevent confusing this pyrimidine derivative with the pyridine analogue of sulfanilamide, has been distributed for experimental use and clinical investigation. The name, sulfadiazine, has been approved by the Council on Pharmacy and Chemistry.

Feinstone and his collaborators (2) have made an excellent report upon the toxicity, absorption and chemotherapeutic activity of this compound in experimental animals. As regards the acute toxicity of sulfadiazine for mice, based upon blood concentrations, they found that the L.D. 50 (i.e., the blood concentration of the drug which kills 50 per cent of the mice) lay between 175 and 200 mgm. per cent. In chronic toxicity studies in monkeys, in which comparisons were again made upon the basis of blood concentrations, they observed that sulfadiazine produced less tissue damage than did sulfathiazole or sulfapyridine. Interesting points which were brought out in this

[1] These investigations have been supported by a grant from the John and Mary R. Markle Foundation.

[2] Calco Chemical Division of The American Cyanamid Co. Fellow in Preventive Medicine.

study were that the blood concentrations resulting from given doses of sulfadiazine in monkeys and in mice were about four times as high as those resulting from comparable doses of sulfapyridine or sulfathiazole, and that the drug existed in the blood primarily in the "free" form because the acetyl derivative appeared to be readily excreted in the urine. They found that this compound had a high degree of therapeutic activity in experimental pneumococcal, haemolytic streptococcal, and staphylococcal infections in mice, and that it was very effective in the treatment of experimental Friedländer's bacillary infections in mice.

Klinefelter (3) has shown, in our laboratory, that sulfadiazine was an effective chemotherapeutic agent in experimental E. coli infections in mice. We have been studying the therapeutic efficiency of sulfadiazine in experimental pneumococcal, haemolytic streptococcal and staphylococcal infections in mice during the past year, and we shall discuss our findings in this report.

METHODS

White mice of the CF1 strain, aged 4 to 7 weeks, were used in all experiments.

Strains of Organisms

The SV1 strain of Type I pneumococcus was employed as the test organism in producing the experimental pneumococcal infections. This pneumococcus produced infections in mice which resulted in 98.5 per cent deaths among the untreated animals, but these infections have been quite susceptible to therapy with certain of the sulfonamide compounds. The survival of one control mouse raised the unanswerable question as to whether the mouse was actually inoculated or whether the survival represented an instance of high host resistance to the infection.

The C203 strain of Group A haemolytic streptococcus was used in producing the experimental haemolytic streptococcal infections in mice. The strain of staphylococcus aureus employed in these experiments was isolated 2 years ago from a patient ill with lung abscess. The methods of producing these infections have been described previously (4).

Drugs

In the pneumococcal infections, the therapeutic efficiency of sulfadiazine was compared with that of sulfapyridine and sulfathiazole. In streptococcal infections sulfadiazine was compared with sulfanilamide, and in staphylococcal infections, sulfadiazine was compared with sulfathiazole. All of these drugs were administered in the diet of the mice and were prepared as follows: To a weighed amount of powdered Purina Dog Chow, sufficient drug to result in the desired concentration

was added with thorough mixing in an electrical mixing machine. The mice were kept in individual cages. The drug-diet mixture, offered in non-spilling containers, was weighed daily in order to ascertain the amount which had been consumed, and from the total amount of the mixture consumed, the daily intake of drug was calculated. Sulfanilamide was administered in the diet for 4 days, and the other

TABLE I

The Effect of Therapy with Sulfathiazole, Sulfapyridine, Sulfanilamide and Sulfadiazine upon the Course of Pneumococcal and Haemolytic Streptococcal Infections in Mice

NUMBER OF MICE	NUMBER OF ORGANISM INOCULATED	DRUG CONCENTRATION IN DIET (PER CENT)	DEATHS—DAYS AFTER INFECTION												SURVIVALS	
			1	2	3	4	5	6	7	8	9	10	11	12	Number	Per cent
Pneumococcus—Type I, Strain SV1																
41	6150	S.T. 1.0*		1		1	2	3	1	1	2				30	73
40	6150	S.P. 0.5		3	2	3	5	6	2		1				18	45
40	6150	S.D. 0.1		2	5	2	3	5	3	2		2			16	40
30	6150	None	1	29											0	0
18	6400	S.T. 1.0		1		1	1		2						13	72
20	6400	S.D. 0.2				1			2	1	1				15	75
10	6400	None	1	4	5										0	0
31	490	S.P. 0.25			9	6	7	3		3					3	9.6
27	490	S.D. 0.25		1	1	3	2	2	1						17	63
20	490	None		16	2	1									0	0
35	437	S.P. 0.5		1		2	5	3	3						21	60
34	437	S.D. 0.5				1									33	97
26	437	None		22	2	1									1	3.8
Haemolytic Streptococcus—Strain C203																
36	190	PABS 0.8			1	1			2	3					29	80.5
37	190	S.D. 0.125			1	2									34	92
20	190	None	13	7											0	0

* S.T., = Sulfathiazole, S.P. = Sulfapyridine, S.D. = Sulfadiazine, PABS = Sulfanilamide.

compounds for 2 days prior to infection. In mice infected with pneumococci and streptococci, treatment was carried out for 5 days after infection, and then the mice were observed for 7 days. In the staphylococcal infections, treatment was continued for 12 days after infection had been produced and the mice were observed for 30 days.

The method of Bratton and Marshall (5) was used for determining the concentra-

TABLE II

The Effect of Therapy with Sulfathiazole and Sulfadiazine Upon the Course of Staphylococcal Infections in Mice

NUMBER OF BACTERIA INJECTED*	NUMBER OF MICE	DRUG	CONCENTRATION IN DIET	MICE DYING (DAYS AFTER INFECTION)																												SURVIVED 30 DAYS	MEDIAN SURVIVAL TIME
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30		
			per cent																														*days*
5.2 billion	15	S.T.**	0.1		2	2	2									1	1		2	2	1											2	13.5
5.2 billion	18	S.D.	0.25			2											2	2		7	1		1	2								1	16.4
5.2 billion	10	None			3	3	2				2																					0	2.66
500 million	12	S.T.	0.1		1															3	3	1	2	2								0	17.66
500 million	15	S.D.	0.1						1							1				1	3		2		1	1		1	3			1	0	19.5
500 million	10	None			3	1		2	1	2	1																					0	4.3

* Injections were by intravenous route.

** S.T. = Sulfathiazole, S.D. = Sulfadiazine.

tions of the various drugs in the blood of mice at certain periods during the feeding experiments. This was done by pooling the hearts' blood of 5 mice for each point. Multiple determinations were carried out to ascertain the concentration of the various drugs in the blood of mice on the 2nd, 5th, and 7th days of therapy. As a result of these experiments it was found that comparable concentrations of the various drugs could be maintained in the blood of the mice when the mice were placed on the following diets: For sulfathiazole, 1.0 per cent; sulfapyridine, 0.5 per cent; sulfanilamide, 0.8 per cent; and for sulfadiazine, 0.1 per cent. Mice fed on diets containing these amounts of the drugs maintained blood concentrations of from 5 to 7 mgm. per cent during the period of therapy.

RESULTS

As may be seen in Table I, sulfadiazine is somewhat less effective than sulfathiazole but equal to sulfapyridine in the treatment of experimental pneumococcal infections in mice when comparable blood levels of the drugs, i.e., 5 to 7 mgm. per cent, are maintained in the experimental animals. If the blood concentration of sulfadiazine is increased to 10 mgm. per cent, as occurs when a diet containing 0.2 per cent of the drug is fed, this drug is as effective as sulfathiazole. With blood concentrations of about 25 mgm. per cent of sulfadiazine, as are obtained by feeding a diet containing 0.5 per cent of the drug, the great majority of infected mice survive.

It is also shown in Table I that sulfadiazine is as effective as sulfanilamide in the control of haemolytic streptococcal infections in mice if both drugs are maintained at a blood concentration of 5 to 7 mgm. per cent.

As may be seen in Table II, sulfadiazine proved to be as effective as sulfathiazole in the control of experimental staphylococcal infections. Although in both experiments, mice treated with sulfadiazine lived slightly longer than those treated with sulfathiazole, statistical analysis shows that the difference might have arisen by chance.

SUMMARY AND CONCLUSIONS

The results which we have described show that sulfadiazine is an effective chemotherapeutic agent in the control of experimental haemolytic streptococcal, staphylococcal and pneumococcal infections in mice.

When equivalent blood concentrations of the drugs were compared,

sulfadiazine was found to be as effective as sulfanilamide in streptococcal infections, and as sulfathiazole in staphylococcal infections, but less effective than sulfathiazole in pneumococcal infections. The inferiority of sulfadiazine to sulfathiazole in the last instance is offset by the greater ease with which relatively high blood concentrations can be produced and maintained with sulfadiazine. When blood levels of 25 mgm. per cent were obtained, by increasing the proportion of the drug in the diet to 0.5 per cent, sulfadiazine gave excellent therapeutic results. Moreover, mice tolerated these higher blood concentrations for periods of at least two weeks with no apparent ill effects. They showed no pathological alterations in spleen, liver or kidney which could be attributed to the drug.

Because it is possible to produce and maintain relatively high blood concentrations of sulfadiazine without injury to the tissues and because such concentrations have a marked therapeutic efficiency, we believe that this drug may prove to be very useful.

We wish to thank the Calco Division of the American Cyanamid Company for the chemotherapeutic agents used in these experiments.

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STUDIES ON SULFADIAZINE

II. The Clinical Use of Sulfadiazine in the Therapy of Bacterial Infections, Other Than Pneumonia[1]

GORDON I. TREVETT,[2] M.D., RUSSELL A. NELSON, M.D., and PERRIN H. LONG, M.D.

From the Department of Preventive Medicine, the Johns Hopkins University, and the Medical Clinic of the Johns Hopkins Hospital

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In 1940, Roblin and his associates (1) described the pyrimidine analogue of sulfapyridine and gave it the name of sulfadiazine. Feinstone and others (2) have reported that this compound shows a high degree of therapeutic activity in the control of experimental pneumococcal, hemolytic streptococcal, and Friedländer's bacillus infections in mice. These observers also noted that it was easy to maintain relatively high concentrations of sulfadiazine in the blood of experimental animals and that these high concentrations produced little if any damage to the tissues of the experimental animals. Klinefelter (3) demonstrated that sulfadiazine was very effective in controlling experimental E. coli infections in mice; and Long, Bliss and Ott (4) have confirmed the observations of Feinstone and his co-workers in respect to the therapeutic efficiency of this drug in experimental infections in mice. In addition they have shown that sulfadiazine and sulfanilamide are about equally effective in hemolytic streptococcal infections of mice when the blood concentrations of the two drugs are maintained at 5 to 7 mgm. per cent.

Plummer and Ensworth (5) studied the absorption and excretion of sulfadiazine in human beings. They concluded from their observations that sulfadiazine was rapidly absorbed, that it was easy to maintain fairly constant levels of the drug in the blood, that the pro-

[1] These investigations were supported by a grant from the John and Mary R. Markle Foundation.

[2] Winthrop Chemical Company Fellow in Preventive Medicine.

portion of conjugated sulfadiazine in the blood was small, and that most of the drug was excreted by the kidney. Reinhold and his associates (6) as a result of their studies thought that the absorption and excretion of sulfadiazine in human beings resembled that of sulfapyridine rather than sulfathiazole, and their observations tended to show that the drug is readily absorbed by most individuals. In their experience only small amounts of acetylated sulfadiazine were found in the blood and the drug was excreted less readily than was sulfathiazole. They noted that sulfadiazine was present in peritoneal and pleural fluids in concentrations approximating those obtained in the blood, while spinal fluid concentrations averaging 50 per cent of the

TABLE I

Blood Concentrations of Sulfadiazine Following Single Peroral Doses in Human Beings

PATIENT	DOSE, GM./KILO P.O.	BLOOD CONCENTRATIONS IN MGM. PER CENT, HOURS FOLLOWING ADMINISTRATION OF SULFADIAZINE													
		1		4		8		12		24		48		72	
		F	T	F	T	F	T	F	T	F	T	F	T	F	T
D.	0.05	2.0	2.0	4.5	4.5	3.3	3.5	2.7	2.9	1.8	1.9	0.9	0.9		
J.	0.05	2.9	2.9	5.7	5.8	3.2	3.8	2.6	2.6	1.0	1.2	0.3	0.3		
A.	0.1	1.7	1.7	7.3	7.5	7.9	8.9	6.8	7.4	5.1	5.8	2.4	2.4		
B.	0.1	2.6	2.6	5.8	5.9	4.8	5.4	3.6	3.8	2.5	2.9	1.1	1.2		
Al.	0.1	0.6	0.6	6.1	6.0*	6.7	6.7	5.8	5.1	3.8	3.7	0.7	0.8	0	0

F = Free Sulfadiazine.

T = Total Sulfadiazine.

* The recovery of acetylsulfadiazine is incomplete so that apparent inconsistencies such as this are occasionally found.

blood concentration were found. They observed that sulfadiazine penetrated the red blood cells far more readily than does sulfanilamide. In a subsequent publication (7) Sadusk and Tredway confirmed these observations. Flippin and his associates (8) reported that the administration of sodium sulfadiazine by the intravenous route produced relatively high blood levels which were well maintained for a period of about eight hours.

We have been studying the absorption, distribution, and excretion of sulfadiazine for the past year. As will be seen in Table I, the administration of single peroral doses of sulfadiazine to human beings is not followed by such a rapid rise in the concentration of the drug

in the blood as is noted following the administration of sulfanilamide or sulfathiazole. Our observations tend to show that the drug is absorbed rather slowly, that its concentration in the blood is well maintained over the first twenty-four hours, and that during this period relatively small amounts of the drug exist in the blood as acetyl sulfadiazine. The apparent reason for the better maintenance of the concentration of this drug in the blood is that sulfadiazine is excreted less rapidly than is sulfanilamide or sulfathiazole. From our observa-

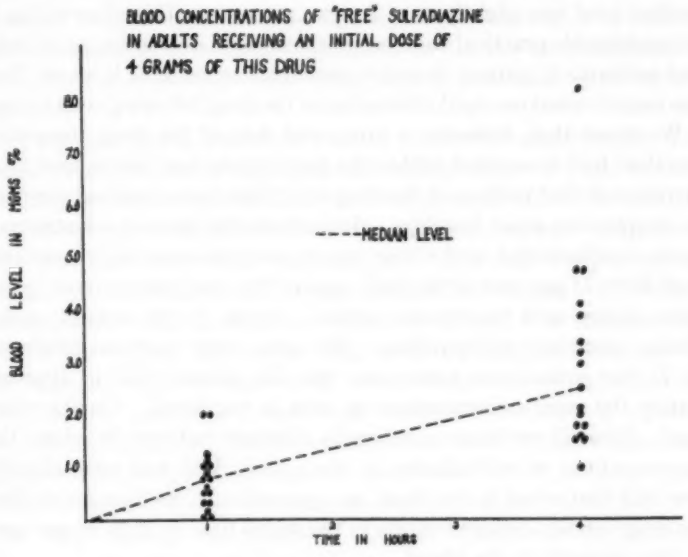

CHART I

tions upon the urinary excretion of this drug, we attribute the small amounts of the acetylated fraction noted in the blood to the fact that acetyl sulfadiazine is readily excreted by the kidney and, hence, does not tend to accumulate in the blood. Another interesting point which is brought out in Table I is that the drug, though well absorbed in doses of 0.05 gram per kilogram, is not absorbed in proportionately greater amounts if the dose is increased to 0.1 gram per kilogram of body weight. As a matter of fact, there was little difference between the blood concentrations, at four hours, of an individual who had re-

ceived 0.1 gram per kilogram and of one who had received half the dose. Thus we found, as did Reinhold and his associates that sulfadiazine, in its manner of being absorbed, more closely resembles sulfapyridine than it does sulfanilamide or sulfathiazole.

In Chart I the median blood concentration of free sulfadiazine noted in seventeen adult patients following the oral administration of 4.0 grams of the drug in tablet form is recorded. It is interesting that one hour after the administration of the drug, the median blood level was less than 1 mgm. per cent, while at the end of four hours, the median level was slightly over 2 mgm. per cent. This observation is of considerable practical value when the method of treating an acutely and seriously ill patient is under consideration because it shows that one cannot count on rapid absorption of the drug following such a dose.

We found that, following a single oral dose of the drug, somewhat less than half is excreted within the first twenty-four hours, and total excretion of that portion of the drug which has been absorbed may not be complete for about five days. In patients who were on maintenance doses of sulfadiazine, and whose urinary outputs were fairly constant, from 60 to 75 per cent of the daily dose of the drug was excreted in the urine during each twenty-four period. Again, in this respect, sulfadiazine resembles sulfapyridine. We agree with previous observers (6, 7) that sulfadiazine passes over into the pleural fluid in approximately the same concentrations as exist in the blood. On the other hand, although we have occasionally observed patients in whom the concentrations of sulfadiazine in the spinal fluid was only slightly over half that noted in the blood, as a general rule, we have found that the drug reaches a concentration in the spinal fluid of 75 to 90 per cent of that present in the blood.

RESULTS OF TREATMENT

During the past year we have treated 230 patients ill with various types of infections, of whom 114 patients were suffering from pneumonia. The results obtained from the use of sulfadiazine in pneumococcal pneumonia at the Johns Hopkins Hospital during the year 1940–41 are reported by Billings and Wood in the following paper (9). It is our purpose to discuss the use of this drug in infections other than pneumonia.

The great ease with which relatively high concentrations of sulfadiazine can be maintained in the blood as well as the notable infrequency of toxic manifestations encountered in preliminary trials, suggested that we might maintain higher blood concentrations with this compound than had been our practice with the other sulfonamides. By so doing a relatively greater therapeutic response would be expected. Subsequent experience has confirmed this hypothesis.

Inspection of Table II will demonstrate that we have had a moderately wide experience in the use of sulfadiazine in the treatment of *hemolytic streptococcal infections*, and although we are able to include only six instances of severely ill patients, we can say that sulfadiazine has been very successful in the control of infections due to this microorganism.

As may be seen in Table III, Part A, in mild or moderately severe hemolytic streptococcal infections (and among these we would include tonsillitis, erysipelas, otitis media, mild scarlet fever, etc.), oral therapy with the drug is to be preferred and the initial dose should be based on 0.05 gram per kilogram of body weight. This may be followed by the dosage outlined. Such therapy in most individuals will produce, within twenty-four hours, a concentration of from 7 to 10 mgm. per cent of the drug in the blood. This level, we think, is adequate for the control of mild or moderately severe hemolytic streptococcal infections. In hemolytic streptococcal infections involving bone, such as otitis media, mastoiditis, or osteomyelitis, the administration of the drug should be continued in small doses such as will produce blood concentrations of about 5 mgm. per cent for a period of at least ten days after clinical cure has been effected. Otherwise a rather explosive recurrence of the infection may result. In severe hemolytic streptococcal infections, we prefer to begin treatment with an intravenous injection of sodium sulfadiazine as outlined in Table III, Part B. Sodium sulfadiazine is prepared and administered in the same manner as has been previously described for sodium sulfapyridine and sodium sulfathiazole (10). It is interesting that, as Flippin and his associates reported, little trouble is encountered in maintaining adequate concentrations of sulfadiazine when therapy is carried out solely by the intravenous route. In most patients one dose of sodium sulfadiazine every twelve hours will maintain adequate concentrations

TABLE II

INDICATION FOR THERAPY	NUMBER OF CASES TREATED	RESULTS WITH DRUG THERAPY		TOXIC REACTIONS*
		Improved	Unimproved	
Beta Hemolytic Streptococcal				
Pharyngitis and Tonsillitis	23	21	2	Fever
Erysipelas and Cellulitis	5	5		
Otitis Media and Mastoiditis	4	4		
Pneumonia	3	3		
Scarlet Fever	2	2		
Peritonitis with Septicemia	2	2		
Meningitis	1	1		Hematuria with fever
Empyema	1	1		
Chronic Osteomyelitis	1	1		
Meningitis				
Meningococcus	3	2	1	
H. Influenza with Sepsis	2		2	Fever with rash
Bacterial Endocarditis				
Subacute	6	1	5	2 Vomiting
N. Pharyngis Sicca	1		1	
Staphylococcal Infections				
Chronic Osteomyelitis	5	5		
Acute Osteomyelitis with sepsis	1	1		
Meningitis	1	1		
Sepsis	1		1	
Abscesses	1	1		
Skin Infections	2	2		Fever
Empyema	1	1		
Urinary Tract Infections				
E. Coli	2	2		
E. Aerobacter	1		1	
Friedländer's	1	1		
Bacteremia				
E. Coli	1	1		
S. Aertrycke	1	1		
Pneumococcal Infections				
Pneumonia	105	Reported by Billings & Wood (9)		Rash Fever Conjunctivitis Leukopenia
Pneumonia treated with serum and another drug	9			
Empyema	2	2		
Pneumonia, Etiology unknown	18	14	4	Hematuria 2 Fever Leukopenia
Miscellaneous	24	9	15	2 Hematuria Rash

* Reactions represent one case unless otherwise indicated.

of the drug in the blood. The doses of the drug which have been outlined in Table III, Part B, will produce concentrations of from 15 to 20 mgm. per cent of the drug in the blood of the patients. Such a blood concentration is desirable in the therapy of severe hemolytic streptococcal infections such as peritonitis, meningitis, very acute or rapidly progressing lymphangitis, or septicemia. We do not believe

TABLE III

The Dosage of Sulfadiazine and Sodium Sulfadiazine in the Treatment of Hemolytic Streptococcal Infections

A. Mild and Moderately Severe Infections
1. Oral Therapy:
Initial Dose: Sulfadiazine—0.05 gram per kilogram of body weight.
Total Daily Dose: Sulfadiazine—0.10 gram per kilogram of body weight divided into six doses and given Q.4 hours, day and night until the temperature has been *normal* for five days.

B. Severe Infections
1. Parenteral and Oral Therapy:
Initial Dose Parenteral: Sodium Sulfadiazine—0.15 gram per kilogram of body weight made up as a *5% solution* in *sterile distilled water*. (*Do not boil or autoclave.*) Administer slowly by the *intravenous* route.
Total Daily Dose Oral: Sulfadiazine—0.15 gram per kilogram of body weight, divided into six equal doses and given at 4 hour intervals, day and night until the temperature has been *normal* for five days. Then decrease dose of drug slowly until patient is ambulatory.
2. Parenteral Therapy:
Initial Dose: Sodium Sulfadiazine—as advised above.
Maintenance Dose: Sodium Sulfadiazine—0.05 gram per kilogram of body weight made up as a *5% solution* in *sterile distilled water*. (*Do not boil or autoclave.*) Administer slowly by the *intravenous* route Q.12 hours. Determine the blood concentration of the drug daily. Concentrations of more than 20 milligrams % are inadvisable. Change to oral therapy with sulfadiazine as soon as possible.

that it is necessary or wise to produce concentrations of the drug over 20 mgm. per cent.

We have had the opportunity of testing the therapeutic effectiveness of the drug in three patients ill with *meningococcal meningitis*. In these patients we have tried to obtain blood concentrations of sulfadiazine of from 10 to 15 mgm. per cent. Two of the patients responded very favorably to the drug, while the other died within one hour after therapy was started. Although it is obvious that no con-

clusions can be drawn from these three cases, they lend support to the observations of Dingle, Thomas and Morton (11), and further encourage clinical trials in meningococcal meningitis.

Six patients suffering from *subacute bacterial endocarditis* have been treated during the past year with sulfadiazine. In these patients blood concentrations of the drug were maintained at from 15 to 25 mgm. per cent. One patient made a dramatic response to therapy and at the time this paper was prepared, had had negative blood cultures for sixteen consecutive weeks and during this period of time had gained 30 pounds in weight. We propose to continue this patient on therapy with the drug for a period of at least six months. The five remaining patients were not materially improved by chemotherapy. In all of these patients, the etiological agents were of the mouth varieties of alpha hemolytic streptococcus.

Twelve patients suffering from various types of *staphylococcal infections* have been treated with sulfadiazine. In five who had chronic staphylococcal osteomyelitis, sufficient doses of the drug were given to maintain a blood level of from 5 to 7 mgm. per cent. All of these patients have made a gratifying response to therapy and all were continued on the drug for a period of at least four months. In the treatment of chronic staphylococcal osteomyelitis, it is our belief that it is best to remove all sequestra as soon as possible surgically, and that the drug should be continued for at least two months after the last sinus has closed. We have not had enough experience with severe staphylococcal infections to warrant a definite statement as to the dosage of the drug that should be used. However, we suggest that blood levels of 15 to 20 mgm. per cent of sulfadiazine should be established and maintained in such infections until the blood has been completely sterilized. It would seem advisable to continue treatment for a long period of time on gradually decreasing doses in order to avoid a recurrence of the infection.

Our experience with *other types of infections* has been so limited that we do not feel justified in attempting to assay the clinical effects of the drug in them. However, we would like to report that Dr. Horace Hodes of the Sydenham Hospital, Baltimore, has, during the past winter, effected a cure by means of sulfadiazine in a patient severely ill with Friedländer's bacillus meningitis and that we have

noted very gratifying results in one patient suffering from a Friedländer's bacillus urinary tract infection, who was treated with this drug.

TOXIC REACTIONS

A prominent feature of sulfadiazine therapy in our experience has been the rarity of toxic reactions even in those patients in whom high blood concentrations of the drug have been maintained. Among the entire group of patients treated at the Johns Hopkins Hospital (125 here reported, and 105 reported by Billings and Wood in the following paper) vomiting has been attributed to the drug in only three instances. A few have been nauseated. No definite cyanosis has been observed. Dizziness, vertigo, lack of power of concentration, and other mild cerebral effects of the drug have been very uncommon. In contradistinction to the report of Flippin and his associates, no instances of "drug psychoses" have been seen. We are at a loss to explain this discrepancy in observations. Drug fever has been infrequent, occurring in only 3 per cent of the patients. They have been of the three general varieties encountered as a reaction to the other sulfonamide compounds. The first was a fever occurring from the fifth to the tenth day which was marked by a very sudden and abrupt elevation of temperature and which was accompanied by aching of the legs and back. The second was a slowly mounting type accompanied by symptoms of mild malaise. The third was a rather rapidly rising, maintained type, accompanied by severe malaise and headache. In the course of our observations on the clinical use of sulfadiazine we have observed an instance of drug fever which was produced in a way that was new to us and which is worth citing. An elderly woman, ill with pemphigus, had acquired a considerable amount of secondary staphylococcal infection in the ruptured blebs. It was decided to try to clear this infection by using a sulfadiazine spray. On the twenty-fourth day of treatment, fever made its appearance and when the drug spray was withdrawn the fever promptly subsided. At the time the fever appeared only a slight trace of sulfadiazine was in the blood. Six days later the resumption of the spray was promptly followed by a rise in temperature which receded shortly after the sprays were discontinued.

Drug rashes with or without fever have occurred in three patients. These rashes have been of the macular variety and not the erythema nodosum type of rash which is so commonly seen as a toxic manifestation of sulfathiazole therapy. Acute hemolytic anemia has not been observed in this group of patients nor have we seen any definite evidence that sulfadiazine will produce slowly progressive hemolytic anemias. Two instances of leukopenia have been noted occurring on the third and seventh days of therapy. In one of these patients the drug was subsequently readministered and did not produce a leukopenia. One instance of mild conjunctivitis, accompanied by congestion of the scleral vessels has been observed which was probably due to sulfadiazine. In four instances hematuria has been attributed to the drug. This complication appeared during the first two weeks of therapy in all instances, and quickly disappeared when the drug was discontinued and fluids forced. There was associated renal pain in two patients. No serious anuria or oliguria, clearly due to the drug, has been observed. Three patients with hematuria have been omitted from this discussion because they are to be reported in more detail later. It seems unlikely that the hematuria in these instances was related to the chemotherapy.

In ten instances we have had occasion to shift immediately to sulfadiazine from therapy with sulfanilamide or sulfathiazole because of the appearance of a rash or fever during the use of the latter compounds. The original toxic manifestations disappeared within twenty-four to forty-eight hours although there was no rest interval before the administration of sulfadiazine was instituted. In one patient who had had a sulfanilamide fever, the shift to sulfadiazine resulted in a drug rash on the tenth day of therapy with the latter drug. These are points of considerable importance because they suggest that patients sensitive to the other sulfonamide compounds will, in general, be able to tolerate sulfadiazine. Similar observations have been made by Finland, Strauss and Peterson (12). In *summing up* our observations upon the toxic effects of sulfadiazine, we may say that with the exception of sulfaguanidine, sulfadiazine has produced many fewer toxic manifestations than have the other compounds of the sulfanilamide group.

SUMMARY AND CONCLUSIONS

Sulfadiazine has proved to be very satisfactory and effective in the treatment of hemolytic streptococcal infections.

The relatively low incidence of toxic reactions encountered in the course of sulfadiazine therapy makes us believe that it is safe to maintain higher blood concentrations of this compound than has been our custom with the other sulfonamides.

The drug shows promise of being effective in the treatment of acute meningococcal and staphylococcal infections, but because our data are scant in this respect we feel that its use in these infections should still be considered as being in the experimental stage.

Because sulfadiazine is well tolerated, it appears to be the best available drug for the treatment of chronic bacterial infections which require long continued therapy.

We wish to thank the Lederle Laboratories and the Calco Division of the American Cyanamid Company for the sulfadiazine and the sodium salt of sulfadiazine used in this study.

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STUDIES ON SULFADIAZINE

III. The Use of Sulfadiazine in the Treatment of Pneumococcal Pneumonia

F. T. BILLINGS, JR. and W. BARRY WOOD, JR.

From the Biological Division of the Medical Department, The Johns Hopkins University School of Medicine

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The results of experimental studies on the properties and therapeutic activity of sulfadiazine have been summarized in the preceding papers (1, 2). The characteristics of this new sulfonamide drug which justify its clinical trial in the treatment of pneumococcal pneumonia are the following:

1. A relatively potent antibacterial action against experimental pneumococcal infections in mice.
2. Comparative ease of absorption from the gastro-intestinal tract.
3. Slow excretion from the body.
4. A low degree of toxicity in both acute and chronic experiments.
5. An acetyl derivative which is present in the blood in only small amounts and is relatively soluble in urine.

During the year beginning July 1, 1940 and ending June 1, 1941, 105 adult patients have been treated with sulfadiazine[1] alone or with sulfadiazine and type-specific antipneumococcal serum in the medical wards of the Johns Hopkins Hospital. It is the purpose of the present paper to analyze the results of this treatment.

PATIENTS TREATED AND DIAGNOSTIC CRITERIA

During the 11 month period covered by this report, 176 adult patients (over 15 years of age) were admitted to the medical service with the diagnosis of pneumococcal pneumonia. Only those patients are included whose pneumonia was confirmed by x-ray, and from whom pneumococci were isolated in the sputum. Every effort was made to

[1] The sulfadiazine was supplied by courtesy of Lederle Laboratories, Inc.

type the pneumococci (Neufeld method) directly from the sputum and after mouse inoculation. Cultures of all patients' blood were taken before treatment was started and were repeated at frequent intervals.

Early in the season, 71 patients with pneumonia were treated with drugs other than sulfadiazine, or received sulfadiazine and another drug during the course of their disease. These patients are not included in the present analysis, but the results of the treatment of all patients with pneumococcal pneumonia will be summarized below for purpose of comparison with previous years.

PLAN OF TREATMENT

Chemotherapy alone: As soon as the diagnosis of pneumonia was established in each case, chemotherapy was begun, either by oral treatment, or by intravenous injection of the sodium salt. The usual peroral dosage of sulfadiazine was as follows: Initial dose, 0.10 gram per kilogram of body weight with a maintenance dose thereafter of 1.0 gram every 4 hours day and night until the temperature had remained below 100°F for 3 days. Determinations of the concentration of the drug in the circulating blood were made at daily intervals, and to maintain effective levels an extra gram was administered or omitted as indicated.

As has been shown in the preceding paper and by the work of Sadusk and Tredway (3) sulfadiazine administered by mouth is not rapidly absorbed. There is, moreover, considerable individual variation in the rate of absorption of the drug. Therefore, in those patients who appeared critically ill on admission and in whom it seemed of the utmost importance to attain an effective blood level immediately, sodium sulfadiazine was given intravenously, according to the following routine.

(a) *Initial dose:* 0.10 gram per kilogram of body weight made up as a 5 per cent solution in sterile distilled water.

(b) *Maintenance dose:* 1.0 gram given by mouth every 4 hours day and night until 3 days after the defervescence.

These dosages were found in a few cases to be inadequate and on the basis of further experience we would recommend the routine outlined by Trevett, Nelson and Long in the preceding paper.

The wide variation of blood concentrations of sulfadiazine in 23 patients with pneumonia receiving the drug orally is shown in Chart I. Also in the same chart, the average levels of sulfadiazine in the blood after oral treatment may be contrasted with those observed in patients receiving an initial intravenous injection of sodium sulfadiazine. It

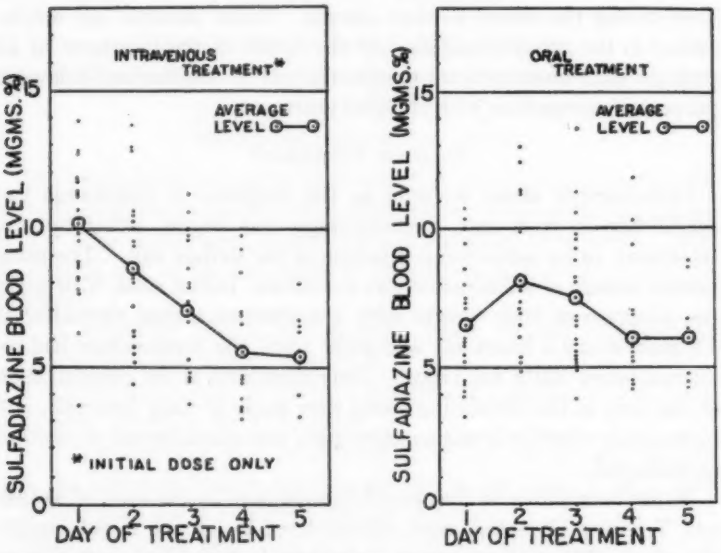

CHART I. COMPARISON OF BLOOD LEVELS OF SULFADIAZINE ATTAINED BY ORAL TREATMENT ALONE AND BY ORAL TREATMENT PLUS AN INITIAL INTRAVENOUS INJECTION OF SODIUM SULFADIAZINE

Each point recorded in the chart represents a single determination, and the points charted for day 1 include all blood levels determined during the first 24 hours of treatment.

is of significance that the drug levels on blood samples drawn during the first 24 hours of treatment in the first group averaged only 6.5 mgms. per cent, whereas in the second group, the average concentration of sulfadiazine was 10.2 mgms. per cent. The importance of this difference, as applied to the chemotherapy of pneumococcal pneumonia, will be discussed below.

In accord with the observations of Sadusk and Tredway determinations of the total amount of sulfadiazine in the circulating blood showed that only small amounts of the drug were normally present in the conjugated form.

Combined treatment with sulfadiazine and type-specific antiserum: In addition to chemotherapy, type-specific antiserum was given when the history, physical findings and laboratory data indicated a poor prognosis. In evaluating the likelihood of recovery the following factors were taken into consideration: The patient's age, the presence or absence of a major concurrent disease, the history regarding chronic alcoholism, the type of pneumococcus causing the pneumonia, the duration of the illness, the number of lobes involved, the leucocyte count, and the presence or absence of jaundice. In most cases in which there was bacteriemia and apparently no response to chemotherapy after 48 hours, the treatment with sulfadiazine was supplemented by the use of type-specific antipneumococcal serum. The dosage of serum was controlled by the Francis skin test (4), and both horse and rabbit sera were employed. The amount of antiserum given varied from 100,000 to 2,000,000 units, the average total dose being 610,000 units.

RESULTS

In Tables 1 and 2 is presented an analysis of the clinical data from the hospital records of 75 patients with pneumococcal pneumonia treated with sulfadiazine alone, and of 30 patients receiving sulfadiazine and type specific antipneumococcal serum.

Patients receiving sulfadiazine alone: Of the 75 patients who received sulfadiazine alone, 56 (74 per cent) had pneumonia due to pneumococci of Types I to VIII, and 7 (9.3 per cent) had bacteriemia. Eight (10.3 per cent) developed complications associated with their pneumonia, and 14 (18.6 per cent) had a major concurrent disease. Only one patient died. On admission he was in peripheral vascular collapse, on the fourth day of his disease, with a positive blood culture of 400 Type V pneumococci per cubic centimeter of blood. He died 9 hours after entering the hospital.

The clinical response to sulfadiazine therapy was usually prompt, but there was wide variation dependent, at least in part, upon the

concentration of sulfadiazine in the blood during the first 12–24 hours of treatment. The average time before the temperature returned to normal[2] in 45 patients whose early sulfadiazine blood levels were above 6.0 mgms. per cent was 30 hours, while in 21 patients whose drug con-

TABLE 1

Analysis of Pneumococcal Pneumonia in Adults Treated with Sulfadiazine

TYPE	NUMBER OF CASES	BACTERIEMIA		COMPLICATIONS OF PNEUMONIA	CONCURRENT DISEASES	TOXIC REACTIONS	NUMBER OF DEATHS
		Number of Cases	Colonies per cc.				
I	14	1	115	Atelectasis (2) Sterile pleural effusion	2	1	
II	6	1	<1	Sterile pleural effusion (2)	3		
III	3						
IV	2				1		
V	19	3	2 2 400	Sterile pleural effusion (3)	2		1*
VI	1						
VII	6	1	7		1	1	
VIII	5				1		
IX	2				1		
X	1						
XII	2						
XIV	3						
XIX	2				1	1	
XX	1						
XXV	2	1	3		1		
XXVIII	1						
Untyped	5				1	1	
Total.....	75	7		8	14	4	1
Percentage....		9.3%		10.6%	18.6%	5.3%	1.3%

* Bacteriemia 400 colonies per cc.

concentration was less than 6.0 mgms. per cent, an average of 39 hours elapsed before their fever had subsided to normal.

The importance of high blood levels of sulfadiazine early in the course of treatment is also well shown by a comparison of the results obtained in two very similar bacteriemic cases summarized in Chart

[2] Below 100°F.

II. The first patient was treated at the outset with intravenous sodium sulfadiazine, a high blood level (10.2 mgms. per cent) was attained promptly, and the blood stream was sterilized within the first 24 hours. In the second case, oral administration of sulfadiazine

TABLE 2

Analysis of Pneumococcal Pneumonia in Adults Treated with Sulfadiazine and Antipneumococcal Serum

TYPE	NUMBER OF CASES	BACTERIEMIA		COMPLICATIONS OF PNEUMONIA	CONCURRENT DISEASES	TOXIC REACTIONS TO SULFADIAZINE	NUMBER OF DEATHS
		Number of Cases	Colonies per cc.				
I	8	3	25	Empyema	5		3(1*)
			32				
			1				
II	2			Sterile pleural effusion			
III	3	1	+	Sterile pleural effusion	2	1	
IV	1	1	1				
V	6	6	32	Empyema	4	1	
			70	Sterile pleural effusion			
			+				
			25				
			42				
			4				
VI	1				1		
VII	4	2	2	Sterile pleural effusion	1		
			75				
VIII	2	2	3	Sterile pleural effusion	2		1*
			1				
IX	1				1		1
XII	1				1		1
XXV	1	1	2		1		1*
Total.....	30	16		7	18	2	7
Percentage....		53.3%		23.3%	60.0%	6.6%	23.3%

* Bacteriemia.

resulted in an initial blood level of only 5.0 mgms. per cent, and the bacteriemia persisted on the second day although it later cleared satisfactorily following serum therapy. This latter patient was the only one among those studied whose blood culture remained positive for more than 24 hours.

Patients treated with sulfadiazine and antipneumococcal serum: An analysis of the records of the 30 patients with pneumococcal pneumonia who received sulfadiazine and antipneumococcal serum (Table 2) reveals that these patients were critically ill at the time of admission to the hospital. Sixteen (53.3 per cent) had positive blood cultures, and 60 per cent had major concurrent diseases. There were 7 deaths, giving a case fatality rate of 23.3 per cent. Of the 7 patients who

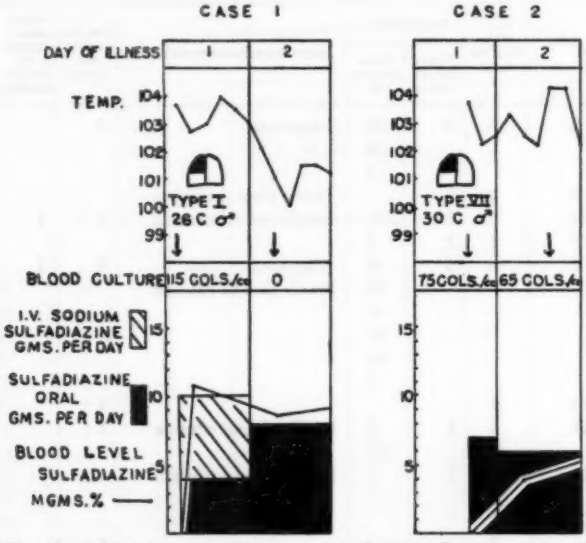

CHART II. EFFECTIVENESS OF INTRAVENOUS SODIUM SULFADIAZINE (CASE 1) IN THE TREATMENT OF BACTERIEMIA AS COMPARED WITH THAT OF ORAL SULFADIAZINE ALONE (CASE 2)

(Arrows indicate time at which blood cultures were taken.) Both patients finally recovered; supplementary serum therapy was employed in Case 2.

failed to survive, 6 had major concurrent diseases, and 4 were in shock at the time of admission to the hospital. Only 3 had positive blood cultures, but 4 of the deaths occurred within the first 24 hours of treatment. The following serious complications were encountered in the 7 fatal cases:

(1) A severe hemolytic anemia due to sulfanilamide given before the patient was admitted to the hospital;

(2) A fatal reaction, possibly anaphylactic in nature, following an injection of antipneumococcal serum;
(3) Uremia caused by bilateral contracted kidneys and obviously unrelated to the chemotherapy;
(4) Marked emaciation from long standing malnutrition and a chronic pulmonary infection;
(5) Uremia with hepatomegaly and splenomegaly present at the time of the patient's admission to the ward;
(6) Chronic alcoholism with cirrhosis of the liver;
(7) Empyema, broncho-pleural fistula, and gangrene of the lung, all of which developed, in spite of intensive chemo- and serotherapy, in a patient suffering from advanced Type I pneumonia.

TOXIC REACTIONS

Among the 105 patients with pneumococcal pneumonia treated with sulfadiazine toxic reactions to the drug were noted only 6 times (5.7 per cent). The toxic reactions included 4 cases of drug fever, one of dermatitis (morbilliform), and one of conjunctivitis with episcleritis. Crystals of the acetylated drug were seen frequently in the urine but in no case were they accompanied by hematuria, or oliguria. Nausea and vomiting were not observed in the present series of cases. The toxic reactions caused by sulfadiazine have been summarized in the preceding paper, where they are discussed in more detail.

Of interest in the consideration of toxic reactions are those patients in whom previously impaired renal function caused delayed excretion of sulfadiazine and a resulting increase in the percentage of conjugated drug in the circulating blood. Chart III depicts the course of such a patient. He was admitted to the hospital with Type I pneumococcal pneumonia and a blood non-protein nitrogen of 70 mgms. per cent. During the first 4 days on the ward he received 24 grams of sulfadiazine. His blood non-protein nitrogen rose rapidly after admission, and at the end of a week the proportion of conjugated drug circulating in the blood amounted to almost 50 per cent of the total. It is significant, that in spite of the high degree of acetylation, excretion of sulfadiazine by the impaired kidneys continued, no further renal damage could be detected, and kidney function gradually returned to normal.

SEVERITY OF PNEUMONIA IN 1940–41 AS COMPARED WITH THAT OF PREVIOUS YEARS

An analysis of the cases of pneumococcal pneumonia observed in the Johns Hopkins Hospital during the past 6 years is summarized in Tables 3 and 4. Apparently the pneumonia encountered in the year

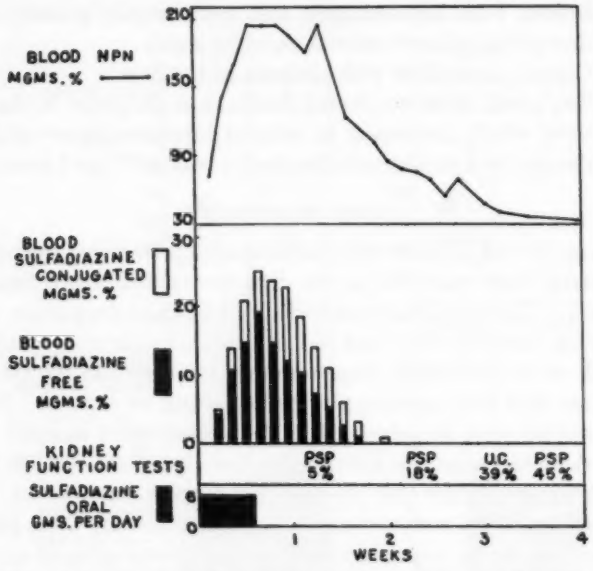

CHART III. A STUDY OF THE EXCRETION AND ACETYLATION OF SULFADIAZINE IN A PATIENT WITH MARKEDLY IMPAIRED RENAL FUNCTION

The patient was a 57 year old colored man (History No. 215210) who entered the hospital on the third day of a Type I pneumonia with bacteriemia. He was treated with both sulfadiazine and antipneumococcal serum and recovered in spite of the renal complications. P.S.P. = excretion of phenolsulfonephthalein in 2 hours. U.C. = Urea clearance (Van Slyke).

1940–41 was, if anything, more severe than that of previous years. Little difference is to be noted in the age incidence of the patients and in the frequency of important concurrent diseases[3], but the number

[3] These included heart disease of various types, nephritis, diabetes mellitus, bronchial asthma, tuberculosis, chronic alcoholism, pregnancy and major surgical operations.

of patients entering the hospital with bacteriemia was significantly greater than in the past 5 years. The final case fatality rate among

TABLE 3

Analysis of Pneumococcal Pneumonia in Adults Treated in the Johns Hopkins Hospital from July 1, 1935 to June 1, 1941

YEAR	NUMBER OF CASES	NUMBER OF CASES WITH BACTERIEMIA	NUMBER OF CASES TREATED WITH						NUMBER OF CASES WITH COMPLICATIONS OF PNEUMONIA	NUMBER OF CASES WITH CONCURRENT DISEASES	NUMBER OF DEATHS
			Serum	Serum and Chemotherapy	Sulfapyridine	Sulfathiazole	Sulfadiazine	Combination of drugs			
1935–1936	157	23 (14.5%)	31 (19.7%)						33 (21.0%)	31 (19.7%)	30 (19.1%)
1936–1937	181	35 (19.3%)	46 (25.4%)						27 (14.8%)	64 (35.3%)	38 (21%)
1937–1938	148	24 (16.5%)	61 (41.2%)						20 (13.5%)	62 (40.2%)	26 (17%)
1938–1939	139	23 (16.5%)	31 (22.3%)	8 (5.7%)	100 (72%)				18 (13.7%)	51 (36.6%)	10 (7.2%)
1939–1940	190	25 (13.2%)	1 (0.5%)	42 (22.1%)	68 (35.7%)	66 (34.7%)		13 (7.0%)	15 (7.9%)	69 (36.3%)	15 (7.9%)
1940–1941	176	37 (21.0%)		43 (24.4%)	8 (4.5%)	46 (26.2%)	75 (41.6%)	4 (2.2%)	17 (9.6%)	66 (37.5%)	18 (10.2%)
— — —	—	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —
Sulfadiazine											
1940–1941	105	23 (22.0%)		30 (28.6%)			75 (71.4%)		15 (14.3%)	32 (30.5%)	8 (7.6%)

TABLE 4

Age Incidence Among Adult Patients Admitted to the Johns Hopkins Hospital with Pneumococcal Pneumonia from July 1, 1935 to June 1, 1941

YEAR	15–19 YRS.	20–29 YRS.	30–39 YRS.	40–49 YRS.	50–59 YRS.	60–69 YRS.	70–79 YRS.	80–89 YRS.
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
1935–36	9.3	29.7	28.2	15.4	10.3	3.8	2.6	0.7
1936–37	8.4	24.3	26.0	16.4	11.9	7.9	4.0	1.1
1937–38	14.2	22.9	17.2	22.0	11.9	8.6	2.4	0.8
1938–39	5.1	22.0	28.8	20.3	8.5	11.0	4.3	0.0
1939–40	7.4	25.8	28.3	16.8	12.4	7.8	1.5	0.0
1940–41	10.9	20.9	30.0	18.5	7.6	9.3	1.7	1.1

all patients treated during the year was the highest recorded since the introduction of chemotherapy in 1938. However, the death rate of 7.6 per cent in the group receiving sulfadiazine and sulfadiazine plus

serum (Tables 1 and 2) compares favorably with that of the previous 2 seasons. A separate analysis of the cases forming the subject of the present report has been included in Table 3 for comparison.

COMMENT

The results obtained during the past year with sulfadiazine have lead us to conclude that this new sulfonamide derivative is as effective a chemotherapeutic agent as sulfapyridine and sulfathiazole in the treatment of pneumococcal pneumonia. This conclusion is in agreement with that recently expressed by Flippin and his associates (5), and by Finland, Strauss, and Peterson (6).

The clinical use of sulfadiazine has served to emphasize several important properties of the drug which distinguish it from the sulfonamide compounds previously used in the treatment of pneumonia. First, though high blood levels are easily maintained because of the relatively slow excretion of sulfadiazine in the urine, the drug is absorbed slowly during the first 24 hours. Therefore, in order to obtain a therapeutically effective blood level in the first few hours of treatment, it is often necessary to administer the drug by vein. Secondly, in our experience patients have been able to tolerate higher blood levels of sulfadiazine with fewer subjective symptoms than has been the case with sulfapyridine and sulfathiazole. Toxic reactions to the drug in the present series of cases were comparatively rare. Thirdly, very little of the sulfadiazine present in the circulating blood is in the conjugated form, significant amounts of the acetyl derivative accumulating in the blood only when there is impairment of renal function. The preponderance of unconjugated sulfadiazine in the blood stream constitutes one of the drug's most important properties, since the acetylated sulfonamide compounds are therapeutically inactive.

In the present study, antipneumococcal serum has been freely administered particularly to patients critically ill at the time of admission to the hospital. Some of these patients no doubt would have recovered had they been treated with sulfadiazine alone, but others, in our opinion, owed their recovery to the combined therapy. Plummer and his associates (7) have recently questioned the advisability of using combined sero- and chemotherapy in the treatment of pneumococcal pneumonia. They were unable to demonstrate any significant differ-

ence in the case fatality rates among patients treated alternately with chemotherapy alone and with chemotherapy and antiserum. In the presence of bacteriemia, the case fatality rates were even higher in the group receiving combined therapy (45.3 per cent) than among the patients treated with drug alone (32.8 per cent). It is of interest, in comparison, that 37 patients with bacteriemia were treated in the Johns Hopkins Hospital during the past year and only 9 or 24.3 per cent died. We would attribute the lower fatality rate to the fact that the antiserum was administered in doses of 50,000 to 100,000 units an hour, that the dosage was controlled by immunological methods (4), and that the total amount given averaged 2 to 3 times as much as that reported by Plummer and his associates. Although the number of cases in both series is too small to be statistically significant, the comparative results suggest that the case fatality rate in the most severe pneumococcal pneumonia may be lowered by employing antipneumococcal serum in addition to chemotherapy, provided the antiserum is administered rapidly and in sufficiently large amounts. In the mild and moderately severe forms of the disease, chemotherapy alone is so uniformly effective that additional serotherapy is seldom required.

SUMMARY

1. Sulfadiazine was employed as the only form of specific therapy in 75 cases of pneumococcal pneumonia. All but one patient recovered.

2. Thirty patients with severe pneumonia, 16 of whom had bacteriemia, were treated with sulfadiazine and type specific antipneumococcal serum. There were 7 deaths, 6 of the fatal cases being complicated by a major concurrent disease.

3. Studies of the absorption of sulfadiazine revealed that the drug was only slowly absorbed during the first 24 hours of therapy. In treating critically ill patients, it was found necessary to resort to intravenous sodium sulfadiazine in order to obtain an effective blood evel within the first few hours of treatment.

4. High blood levels of sulfadiazine were observed to be easily maintained and well tolerated. Only a small fraction of the circulating drug is normally acetylated and the incidence of toxic reactions in the present series of cases was but 5.7 per cent.

5. It is concluded that sulfadiazine is as effective a therapeutic agent in pneumococcal infections as are sulfapyridine and sulfathiazole. This new sulfonamide compound possesses certain pharmacological properties which at present make it the drug of choice for the treatment of pneumococcal pneumonia.

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EXPERIMENTAL SHOCK[1]

I. Effects of Acute Hemorrhage in Healthy Dogs

PHILIP B. PRICE, C. ROLLINS HANLON,[2] WILLIAM P. LONGMIRE[3] AND WILLIAM METCALF[4]

From the Department of Surgery, Johns Hopkins Medical School

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The problem of shock is so complex that no completely satisfactory explanation seems attainable by a limited experimental approach. Rather, the problem demands a coordinated, many-sided attack embracing the investigation of numerous physiologic variables in the organism subjected to shock. Accordingly, in 1938, we undertook the induction of acute circulatory depression in dogs by many different methods, studying each animal intensively before and after "shock" had supervened. It was our hope that a comprehensive experimental study with later analogous clinical studies would permit more satisfactory definition of the term shock and resolution of the condition into useful clinical types, each with its characteristic physiologic and pathologic picture and rational therapy.

In this communication we record the effects observed when healthy dogs are subjected to acute blood loss, and suggest why untreated animals do not recover from large hemorrhages, but, rather, go into fatal "shock." Effects of therapy will be reported separately. Included in this first paper is an account of specific technics employed in our experiments and methods used to assemble and analyze our data.

No attempt is made to review the extensive literature of shock, since this has been done admirably by Cannon (1), Orr (2), Blalock (3), Moon (4), Scudder (5), Harkins (6), and many others. We shall not

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[2] William Stewart Halsted Fellow in Surgery, 1939.

[3] Hunterian Fellow in Surgery, 1939.

[4] Fellow in Surgery, 1938.

even indicate, as a rule, wherein our observations and conclusions agree or disagree with those of other workers. To do so would prolong our presentation, unnecessarily for those well acquainted with the field, tediously for those who are not. We shall limit ourselves to simple statements of our experimental results, and to attempts at interpretation of them. Our debt to other investigators is obviously very great.

EXPERIMENTAL METHOD: TECHNICS AND CRITIQUE

Animals:—Dogs weighing 9 to 27 kg., (usually 15 to 17 kg), were used. They were not limited as to breed or sex, but attempts were made to exclude any that were not healthy, vigorous, and fairly well nourished. Pregnant and lactating dogs, those in heat, and those with active local infections were avoided.

Preliminary observations:—Animals intended for experiments were kept under observation for several days, during which repeated measurements were made of weight, blood cell,plasma ratio, leukocyte count, plasma proteins, systolic blood pressure, and, in some cases, food and water intake. Blood samples during this period were taken without stasis from superficial leg veins.

Anesthesia:—Veterinary nembutal solution (Abbott Co.) was used in most of the experiments. Initial doses were injected slowly into a vein in amounts just sufficient to produce unconsciousness and muscular relaxation; small reinforcing doses were given intramuscularly as needed. We tried to maintain about the same level of anesthesia throughout the experiments, the criteria being quiet sleep, regular respirations (over-dosage causes slow breathing), absence of muscular response to pinching the skin, and presence of knee-kick. Morphine and atropine were not used. A few experiments were carried out under local novocain anesthesia, and in some instances non-traumatized dogs were permitted to awake during the experiment.

Valid interpretation of the observed results of experimental shock requires among other things that contributory effects of the anesthetic employed be known and taken into account. Control studies and analysis of our experiments with and without anesthesia indicate that nembutal *per se* has the following effects in dogs:

Mean arterial blood pressure, body temperature, and hematocrit values are depressed initially, followed by slow recovery to levels below those observed before anesthesia. The severity and duration of these reactions depend upon the size of the dose and, apparently, the animal's individual susceptibility to the drug. Small increases in plasma volume and large reductions in circulating blood cell volume also occur. The spleen enlarges. There is no appreciable change in total intravascular plasma proteins. Respiratory exchange, oxygen uptake, and cardiac output are somewhat lower and considerably more stable in the sleeping than in the waking state. These changes are of sufficient magnitude to make it important to delay the shocking procedure under investigation until new levels under anesthesia have been established, which may require 1½ to 4 hours or longer. Control

experiments indicate that these new levels once reached tend to be well maintained (figure 1), and that small reinforcing intramuscular injections of nembutal do not change them appreciably. They are affected, however, by pronounced variations in depth of anesthesia.

Basal studies:—Before each experiment the dog, having been denied food, but not water, for at least 18 hours, was reexamined for signs of ill health and was weighed. As soon as he was asleep, operative procedures were carried out incident to cannularization, catheterization, and exposure of vessels required for injections, bleeding, venous pressure, and like purposes. Operative trauma was kept to a minimum, and all blood loss was measured accurately. Table 1, which gives details of a typical experiment, shows that a few tests were made before the anesthetic was administered, and many more afterwards, in order to obtain basal values. These control periods were continued until all specimens necessary for such studies had been collected, and until any immediately observable effects due to anesthesia and operative trauma had become stabilized. This part of our experiments required 2 to 7 hours, averaging about 3. Six control experiments were performed in which the procedures just described were instituted and continued without interruption for as long as 27 hours. These experiments indicate that basal conditions of anesthesia, posture, periodic blood sampling, water deprivation, and the like, although they caused very gradual decrease in blood pressure and plasma volume, probably played relatively little part in the major changes observed to follow acute hemorrhage and other shocking procedures. (See figure 1.)

Induction of shock:—In the present investigation bleeding was the method used. It was carried out in a number of ways,— in large and small amounts, rapidly and slowly, steadily and intermittently, from arteries and from veins; but the method chiefly employed was a massive, venous, protracted bleeding requiring 1 to 2 hours, which was thought to simulate a form of hemorrhage frequently associated with clinical shock. A useful apparatus for the purpose is illustrated in figure 2. Our aim was to remove amounts of blood that would be certainly but not immediately fatal. To accomplish this purpose the animals were bled cautiously to a point where the arterial pressure showed no tendency to rise when hemorrhage was interrupted. Sometimes this point coincided with cessation of blood flow from a cannula in the femoral vein; at other times it was necessary to draw additional blood from an artery.

Methods of producing "shock" other than by hemorrhage will be described in papers devoted to those subjects.

As shown in Table 1, all observations and tests were continued until the animal either died or was well on the way to recovery. Survivors were used for studies of blood regeneration and reestablishment of water and nitrogen balance.

Weight:—Body weight was measured, immediately before and after experiments, on balance scales having an accuracy of ± 10 gms. Exact weights of urine and feces expelled, blood removed, and fluids injected during the experiments were determined. From these data insensible fluid loss and water balance were calculated.

Arterial blood pressure:—During anesthesia blood pressure was measured by means of carotid cannula, mercury manometer, and kymograph. The apparatus shown in figure 3 was used. In the intact animal systolic pressure in the tail was measured by means of the plethysmograph described in figure 4. Results of the two methods are not always parallel, although it happens that in the normal dog caudal systolic and carotid mean pressures are often nearly equal. In this and

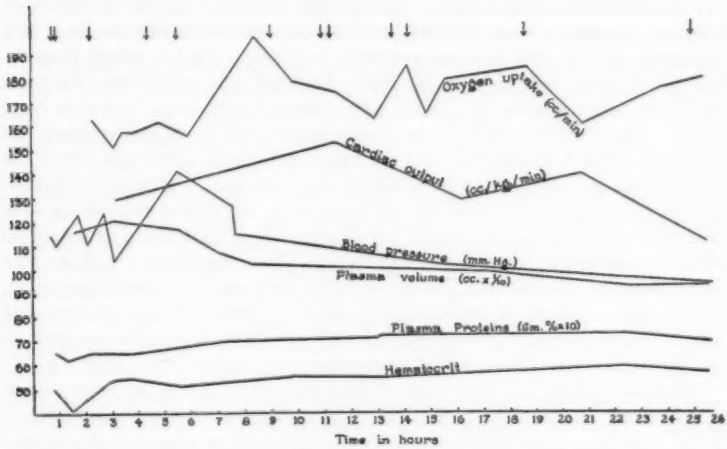

FIG. 1. A CONTROL EXPERIMENT SHOWING SOME OF THE EFFECTS OF PROLONGED ANESTHESIA, MINOR OPERATIVE PROCEDURES AND BLOOD SAMPLING

Dog's weight, 22.52 kg. Nembutal was given at times indicated by the arrows; the first injection, 8 grains (8 cc.) intravenously; subsequent injections, 1.6 to 3.0 grains intramuscularly. The depth of anesthesia was varied. Cardiac output was determined every 4 hours; hematocrit, plasma volume and proteins, and oxygen uptake were measured hourly; blood pressure was recorded continuously. Blood removed in sampling totalled 188 cc. Urine output was fairly constant throughout the experiment—697 cc. altogether. Insensible loss of fluid was estimated at 365 cc. No fluid, blood, or other treatment was given during the experiment. The dog survived, apparently without ill effects.

subsequent papers the unqualified term "blood pressure" will refer to mean end-pressure in the carotid or the femoral artery obtained by damping the manometer as indicated in figure 3.

Venous pressure:—This was measured with a salt or citrate solution manometer, the needle, occluded at the end but having side openings, lying in the exposed, unobstructed femoral or jugular vein. Point of reference was the level of the right

auricle, checked at autopsy. Pressures were uniformly lower in the jugular than in the femoral vein. In our experience, measurements of very low venous pressure are of doubtful accuracy.

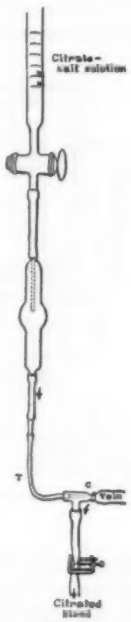

FIG. 2. A SIMPLE APPARATUS WHICH PERMITS VENOUS BLEEDING AT ANY DESIRED RATE WITHOUT CLOTTING

Sodium citrate solution is delivered in measured amounts from the burette, and is carried by means of a fine rubber tube and capillary glass tip to the mouth of the T-shaped cannula, C. This fluid mixes with the blood which is flowing toward the stem of the cannula. By controlling the flow of both citrate solution and citrated blood, any desired rate of bleeding can be established and maintained for long periods of time. If bleeding is to be interrupted temporarily, it is well to close off the vein near the cannula with a small bulldog clamp and flush out the cannula and delivery tube with citrate. The volume of blood removed is estimated by subtracting the amount of citrate solution used from the total amount of citrate blood collected.

Peripheral volume flow of blood in the foreleg was observed by means of a water-filled plethysmograph connected to a sensitive water manometer and kymograph. Water temperature (35° C.) and pressure (atmospheric) were kept constant. Con-

striction of vessels proximally was effected by an air-pressure cuff around the leg so arranged that it could be very rapidly distended or deflated to the desired degree. A special clamp was designed to immobilize the leg without interfering with its circulation.

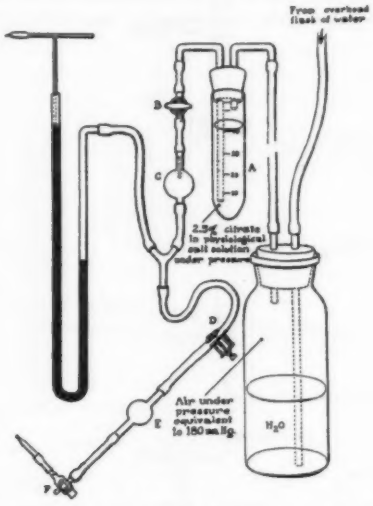

FIG. 3. APPARATUS USED TO PREVENT CLOTTING IN CAROTID CANNULA AND MANOMETER TUBE WITH VERY SMALL MEASURED AMOUNTS OF CITRATE SOLUTION

If the tube is strongly damped at D, and blood pressure is constant, a few drops of anticoagulant let through the stopcock B every hour or so is sufficient to prevent clotting. More citrate may be required if the blood pressure is irregular or is rising, but none at all if it is falling. In estimating the amount of citrate solution injected into the blood stream during an experiment, it is necessary to take into account the amounts contained in the tubing. If blood should happen to back up into the tube past the trap, E, it is easily washed out through the stopcock, F, with solution from A.

For our purpose this method has many advantages over the less physiologic one of direct perfusion. Changes in rate of flow are readily demonstrated. Calculations based on this test have a relative value, but it is doubtful whether they serve as an absolute measure of blood flow in the opposite, undisturbed leg.

Blood sampling during experiments was greatly facilitated by an arrangement shown in figure 5. In this manner any number of samples of any desired size could

be taken uniformly, on the minute or second, without trauma, loss, or risk of clotting or hemolysis. The procedure was easily adapted to collection of samples under oil. The blood was transferred immediately to small bottles, properly numbered and stoppered, containing measured amounts of dry anticoagulant. For most tests we used a mixture of ammonium and potassium oxalate (4 mgm. for each

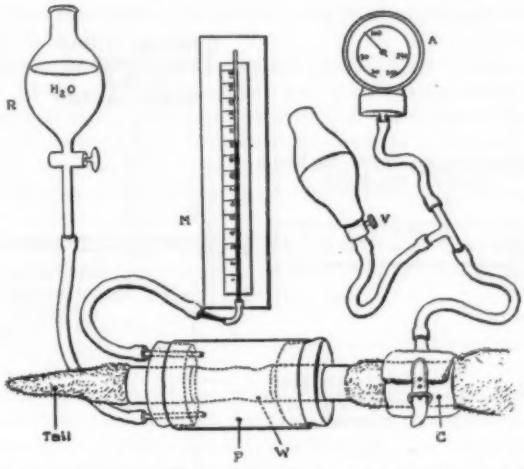

FIG. 4. AN APPARATUS FOR ESTIMATING SYSTOLIC PRESSURE IN A DOG'S TAIL

Adapted from one used by Williams, Harrison and Grollman (7) to measure blood pressure in rats. A plethysmograph, P, with inner flexible wall, W, is filled with water from a reservoir until the fluid rises to a height of 10–15 cm. in a small-bore manometer. An air-pressure cuff, C, is applied to the tail proximally and is rapidly inflated to a pressure of about 200 mm. Hg. This pressure is then slowly released through needle-valve V until water in the manometer shows a sudden rise, indicating passage of blood into the distal portion of the tail. Air pressure in the cuff at such a time is considered a measure of systolic blood pressure. The method is not very accurate, though results improve with practice.

cc. of blood), in a proportion of 13 to 7, a combination said (8) to have minimal effects upon corpuscular volume.

Plasma/cell ratio:—Wintrobe's (9) hematocrit tubes (1 cc.) were filled without delay from the well shaken specimen bottles, were capped, and were spun horizontally at approximately 3000 R.P.M. for 45 minutes. In this manner a nearly maximum, uniform degree of packing was obtained. Upper levels of white and red cells were measured to tenths of a per cent, a hand lens being used if necessary.

The amount of plasma remaining between the cells was considered to be 4 per cent (Gregersen and Schiro(10)). Not infrequently three layers of cells were encountered (see Table 1), especially in the blood of "shocked" animals,—the column of red cells, the cap of platelets and white cells, and between them a clearly demarcated reddish segment. Smears showed this intermediate layer to be predominantly white cells; indeed, a fair degree of correlation was found between the combined

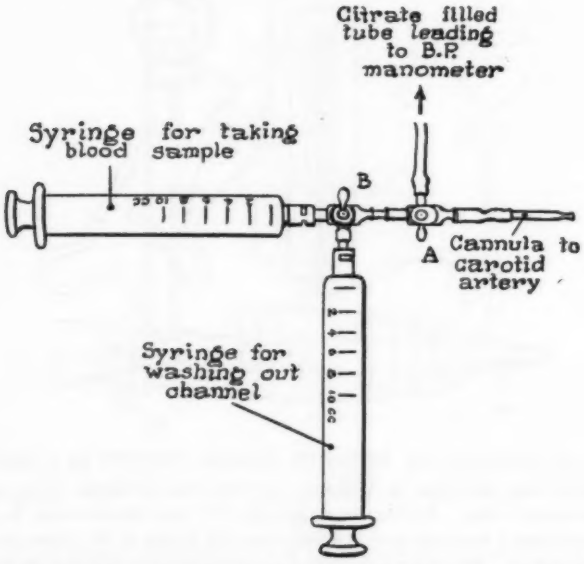

FIG. 5. A USEFUL ARRANGEMENT FOR TAKING BLOOD SAMPLES FROM THE CAROTID CANNULA

First, stopcock A is turned toward the syringes and about 5 cc. of blood are drawn into the lower syringe to clear the channel of all citrate and diluted blood. Stopcock B is then turned and the blood sample is taken. Turning B to its original position, the contents of the lower syringe are returned to the blood stream. Finally A is turned so as to reconnect the cannula with the manometer. If hemolysis is to be avoided, stopcock B and the sampling syringe should be perfectly dry.

thickness of the mixed and white layers of cells and the leukocyte count of the blood. The significance of this mixed layer of cells is not clear. In calculating circulating blood cell volume (to be discussed later) from plasma volume and hematocrit we used the entire volume of packed cells, both red and white, but corrected

for plasma in the interstices; in studying average corpuscular volume, however, or total red cell volume, the mixed cell layer was considered white.

Hemoglobin was measured by the method of Evelyn and Malloy (11, 12), a photoelectric colorimeter being used.

Blood cell counts were made by standard methods, and for the most part by the same observer. But the red cell count is felt to be at best an inexact method of measuring hemoconcentration, the intrinsic error being much larger than is generally believed (13).

Plasma proteins:—The falling drop method (14, 15, 16, 17) was the one generally employed. Effects of the anticoagulant upon specific gravity were taken into account, and a correction factor for hemolysis (35) was applied whenever necessary. Parallel plasma protein determinations by means of chemical analysis led us to conclude that the comparatively simple falling drop method is sensitive and accurate in showing relative changes in protein concentration, although absolute values may be open to question.

In this investigation we have been concerned not only with protein concentration but also with *total plasma proteins*; that is to say, the total quantity of intravascular plasma proteins, estimated by the formula:

$$\frac{\text{plasma volume (in cc.)}}{100} \times \text{protein concentration (in gm. per cent)}$$

Such determinations are valid provided concentration of proteins in plasma is uniform throughout the vascular bed. That assumption is strongly supported by the discovery that blood samples taken simultaneously from the carotid artery, jugular, femoral, and splenic veins, and the right auricle have approximately equal concentrations of these proteins.

Plasma volumes were estimated by injecting known quantities of the blue dye T-1824 into the blood stream, and measuring the resultant concentration of the dye in plasma by means of a photoelectric colorimeter. Simple in principle, the method in practice is quite the reverse owing to the effects of a number of uncontrollable variables. To the procedure developed by Dawson, Evans and Whipple (18), Gregersen (19, 20), Gibson (21, 22), and others, we have contributed certain refinements which we believe have added to its accuracy and usefulness, particularly in following closely changes in plasma volume over a period of time. A separate paper will be devoted to this technical subject.

Fluid shifts into and out of the vascular bed, or rather net gains and losses of water by plasma, were followed throughout our experiments by noting the differences between observed and expected plasma volumes. Observed plasma volumes are independent estimates made from concentrations of dye in blood samples. The expected plasma volume at any point in the experiment is the original volume corrected for amounts of plasma known to have been removed from or added to the blood stream.

Blood volume:—The formula ordinarily used to calculate blood volume from plasma volume and hematocrit should be corrected to read

$$\text{B.V.} = \frac{\text{P.V.}}{100 - (\text{Ht.} \times 0.96)}$$

since 4 per cent of the plasma is trapped in the column of red cells(10). A much more serious error still obtains, however. Blood may be considered in four categories: (1) actively circulating blood, (2) slowly circulating or stagnant blood (for example, in the capillaries of cold extremities), (3) stored blood (for example, in the splenic pulp), and (4) extravascular blood or blood elements. With the last we are not now concerned. Since the dye T-1824 diffuses readily in plasma, it soon becomes almost uniformly distributed, as can be shown, throughout the vascular bed. Consequently, volume estimates from dye are of the entire quantity of intravascular plasma. Erythrocytes, on the contrary, are unevenly distributed. In actively circulating blood of normal subjects they appear to have a fairly uniform concentration, at least in the larger vessels; in slowly moving or stagnant blood they may or may not have a somewhat higher concentration; in the spleen they may be highly concentrated in relatively small amounts of plasma. To divide the full amount of plasma, therefore, by the proportion of plasma (100 − Ht.) in rapidly moving blood of large vessels, whence our samples, gives a value that is meaningless.

By means of dye it is possible to estimate the volume of all intravascular plasma, but not actively circulating plasma alone. The carbon monoxide method, on the other hand, probably measures only the volume of actively circulating erythrocytes which come in contact with the gas in the lungs. In our opinion neither of these methods (with the hematocrit) measures total blood volume. Estimates of blood volume from body weight may be grossly inaccurate.

The dog's spleen is capable of storing surprisingly large quantities of erythrocytes in concentrated form; it can empty part or all of its store into the blood stream, and almost as quickly re-store cells. Consequently, the peripheral blood may show large variations in blood cell concentration, as measured by hematocrit, hemoglobin, or cell count, without any appreciable change in plasma volume or plasma protein concentration. In non-splenectomized dogs, at any rate, the degree of cell concentration does not constitute a reliable index of fluid shifts or changes in plasma volume.

Circulating blood cell volume:—Because of uneven distribution of erythrocytes, the formula

$$\frac{\text{P.V.}}{100 - (\text{Ht.} \times 0.96)} - \text{P.V.} = \text{C.V.}$$

(P.V., plasma volume; C.V., cell volume) is misleading. It probably comes nearer to being the volume of circulating (unstored) cells, but how near, it is impossible to say. On the other hand, a rise in the hematocrit value of blood flowing in large vessels without commensurate reduction in plasma volume clearly indicates a redistribution of erythrocytes in the vascular system and an increase in the total

mass of *circulating* cells. Such changes are important. It is useful to express them quantitatively. We have used this formula, therefore, not as an absolute measure, but, in lieu of a better way, to measure relative changes in the absolute volume of circulating blood cells.

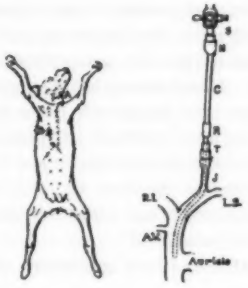

FIG. 6. METHOD USED TO OBTAIN REPEATED SAMPLES OF MIXED VENOUS BLOOD

A length of ureteral catheter, C, is passed through an opening in the left jugular vein, J, to the level of the right auricle. A tightly fitting rubber cuff, R, is so set that the catheter will descend to the proper level each time. Another short piece of rubber tubing, T, is tied into the vein so as to permit smooth passage of the oiled catheter without leakage of blood or entrance of air. With the left foreleg drawn well upwards, the venous channel is almost straight. False passages into the subclavian, innominate or azygos veins (LS, RI, AV) are uncommon and can be readily recognized and corrected when they do occur. The upper end of the catheter is connected to a stopcock and two syringes. One syringe contains oil under which the specimen is collected; the other aspirates blood in order to wash out the catheter before the sample is taken, and immediately afterwards returns this blood to the animal without any loss. The distance the catheter is to be inserted is determined by measuring a line outside the dog's body from the opening in the jugular vein, A, to a point, B, which is directly anterior to the junction of the venae cavae. B is located by taking a point on the right sternal margin at a level which is 60 per cent of the distance from the upper end of the manubrium to the lower end of the gladiolus. After each sample the catheter is removed entirely from the vein (which is closed meanwhile with a small bulldog clamp to prevent leakage of blood or aspiration of air) in order to clean it thoroughly, wet the channel with citrate solution, and oil the outer surface.

Blood chemistry:—The following methods were used: for plasma NPN, the method of Folin and Wu adapted to photoelectric colorimetry (23, 24); for alkali reserve, Van Slyke's technic (25); for sodium and chlorides, modified Butler-Tuthill and Volhard-Harvey methods (25); for plasma potassium, Shohl-Bennett's

chloroplatinate technic (25) and Hoffman and Jacob's adaptation of Kramer and Tisdall's cobaltinitrite method to the photoelectric colorimeter (26, 27).

Respiration:—Throughout each experiment the dog's trachea was connected by tied-in cannula or balloon-tipped tracheal tube to a Sanborn metabolism tester. Most of the time the animal was permitted to breathe atmospheric air as usual; but whenever desired, by the turning of a valve, oxygen uptake could be measured, the chart at the same time recording the respiratory rate and minute volume exchange (figure 11). Blood for arterial oxygen and carbon dioxide content was drawn under oil from the carotid cannula. Mixed venous blood for gas analysis was obtained by means of a catheter passed down the jugular vein to the junction of the superior and inferior venae cavae. (See figure 6 for details of apparatus and technic.) In our hands this method proved to be more dependable and less traumatic than aspiration of the right ventricle through the chest wall. Position of the catheter was checked occasionally by fluoroscope, and always at autopsy. The gas analyses were made by the Van Slyke technic (25).

Cardiac output was estimated by direct application of Fick's principle.

$$\text{Minute volume output} = \frac{\text{Oxygen uptake per minute}}{A_{O_2} - V_{O_2}}$$

Lymph was collected (in a few cases) by direct cannularization of the thoracic duct, coagulation being prevented by means of heparin in the cannula.

"Available" body fluids:—Crandall and Anderson's modification (28, 29) of Hoffmann's thiocyanate method was used. Certain refinements were adopted, such as precise measurement of the volume of thiocyanate solution injected, standardization of the final steps of the test as regards time (since the color tends to fade slowly), and employment of a specially made, acid resistant, gold-coated plunger in the colorimeter. Even so we have not been able to reduce intrinsic technical errors to less than ± 3.3 per cent,—a matter of several hundred cubic centimeters in estimates made on a large dog. Furthermore, a lag due to the slow mixing time of thiocyanate in the body, and variations in the "disappearance rate" with changes of renal activity, are troublesome factors in interpreting concentrations found in plasma. And finally, it is by no means certain how widely or uniformly thiocyanate is distributed in the body. Hence, it is doubtful what the values obtained really mean.

After extensive trial we have concluded: (1) that this test, carefully performed, gives a volumetric value that represents a certain delimited portion of the body fluids, since reinjection of sodium thiocyanate in the same normal animal will give approximately the same value; (2) that large changes in such a reservoir can be detected by repeated injections of thiocyanate and independent calculations; but (3) that minor changes in its volume cannot be accurately measured by this means, nor can rapid changes in volume be followed closely, as is possible in the case of plasma when the dye method is used.

Urine:—In most of the experiments a retention catheter in the bladder was at-

tached to an apparatus which recorded automatically the minute volume output of urine and facilitated collection of samples for examination. In experiments designed to study nitrogen metabolism in relation to shock (35), female dogs were used, the bladder being catheterized and irrigated periodically. Total urine nitrogen was measured by the Kjeldahl digestion method (25).

Necropsies:—These were performed immediately after death. In a few cases, the abdomen and chest of "shocked" animals were opened just before death to see whether any of the gross changes commonly noted at autopsy had occurred at or even following death. Thorough gross and microscopic examinations were made of all organs and tissues, including the brain.

Conduct of experiments:—Each worker kept his own record of observations and results, accurately timed; these, together with data obtained from kymograph records, were assembled finally into a master protocol for each experiment. A typical example is reproduced in table 1. Although we used large dogs, blood lost in operating and sampling was reduced to a minimum. Obviously this was an important consideration in experiments where methods other than hemorrhage were employed to produce shock.

Statistical analysis:—Thirty-seven dogs were used in the present study, but, as will be evident in the following section, not all the tests were made on all the dogs. We believe that the relatively large number of observations made at frequent intervals on each animal has contributed to the significance of the results and the reliability of the curves obtained.

In the interest of lucidity and accuracy, we shall express our numerical results mainly in the form of averages (arithmetical means), but follow them parenthetically, where it seems indicated, with certain statistical data,—number of observations (n), range of variations (R), and standard deviation (σ).

EFFECTS OF ACUTE HEMORRHAGE UPON DOGS

Thirty-two dogs were bled until the arterial blood pressure fell to about half the basal level and failed to rise spontaneously when bleeding was interrupted. Periods of hypotension followed, which ended fatally in 16 untreated dogs; in the remainder death appeared certain when therapy was instituted. The bleedings averaged 35.8 cc. per kg. of body weight (n 32, R 20.2–58.9 cc., σ 9.2 cc.), including blood lost in minor operative procedures and in sampling. Additional blood removed by sampling during the "shock" period averaged 0.9 cc. per kg. Average duration of the hypotensive period from the end of bleeding to death in the untreated animals was 127 minutes (n 16, R 35–400 min., σ 91 min.). Five animals were bled large but sublethal amounts.

Effects of massive hemorrhage upon dynamic aspects of the circulation:—The initial responses of the arterial blood pressure varied. When

TABLE 1

Master Protocol of a Typical Experiment Designed to Show the Effects of Massive Hemorrhage Followed by a Saline Infusion

TIME	TEMP. RECTAL	PRESSURE		SPEC. NO.	CONCENTRATIONS IN BLOOD							VOLUMES			SHIFTS			"AVAILABLE" FLUID		URINE CUMUL. TOTALS	OXYGEN				CARDIAC OUTPUT	CO_2		RESP. VOL.	CUMULATIVE TOTALS		
		Art.	Ven.		Hematocrit			Hgb.	RBC count	Plas. prot.	Dye	Plasma	Circul. cells	Total protein	Water	RBC	Plasma protein	Thiocyanate	Estimated vol.		O_2 Uptake	A_{O_2}	V_{O_2}	Coeff. utiliz.		Ven.	Art.		Blood removed	Fluid injected	
					Red	Mixed	White																							
	°F.	mm. Hg	cm. H_2O					gm. %	millions	gm. %	L620	cc.	cc.	gm.	cc.	cc.	gm.	L490	cc.	cc.	cc./min.	cc. %	cc. %		l./min.	cc. %	cc. %	l./min.	cc.	cc.	
8:25	102.3	132(t)		Ven.	41.2		0.9	11.3	5.91	6.26																			4		Blood sample by vena puncture. B.P. by tail
41																														6	Nembutal sol. (1 grain per cc.) 5.7 cc. i.v.
9:26																															Nembutal sol., 2.0 cc. i.m.
35		112(t)																													Nembutal sol., 2.0 cc. i.m.
50	101.4																														Dog being cannulated; no blood lost
57																		[.390*]	6570											11	Sod. thiocyanate sol. (5%) 5 cc. i.v.
10:17				0	41.5		0.5	11.4	6.84	6.00								.385											9		
19		116									[.562*]	599	461	35.95	0	0	0												16	Dye T-1824 sol. (0.1%) 5 cc. i.v. Carotid B.P.
34		116		1	42.6		0.3	11.8	5.62	6.08	.541	605	525	368.0	+6	+66	+0.85	.382											14		
39				2	42.7		0.3	11.9	6.20	6.07	.530	611	470	370.5	+15	+13	+1.28	.385											19		
44	99.6			3	41.8		0.5	12.3	6.52	6.05	.530	600	440	363.0	+7	−15	+0.89	.385		—									24		Bladder emptied by catheter; 70 cc. urine removed
49				4	41.4		0.6	11.9	5.62	6.08	.531	593	428	36.15	+3	−25	+0.74												29		
55																					74	20.7	16.2	21.8	1.64	42.5	40.2	0.63	37		
11:15	99.4	119																		4											
23			9.5																		69	22.2	16.2	27.1	1.15	38.0	36.0	1.67	45		
35				5	45.3	0.2	1.0	12.8	6.72	6.10	.514	556	484	33.93	−22	+41	−0.75	.382											50		Bleeding from femoral vein started at 11:37
39		114																		14											
45	99.3		9.2																												

45	99.3		9.2																													

12:15	99.4	100		6	45.0	0.2	0.8	12.7	7.29	5.67	.449	493	669	27.95	+7	+237	−1.52	.369		20									220		Blood sample 5 cc.
20																														255		Bleeding interrupted (for 20 min.)
25																					68	20.8	12.8	38.4	0.85	40.9	37.8	1.61	263		
31		89	7.4																													
40		94																														Slow venous bleeding resumed
45	99.4																			20												
59		80																														
1:13																													333		Bleeding interrupted again (for 17 min)
16	100.6			7	43.2	0.3	1.0	13.0	7.17	5.52	.394	426	345	23.50	+18	+43	−1.66	.362		22	67							1.61	338		
19		78																														
30		82																														Bleeding resumed
42	100.6																			24	63							1.73			
52		69	1.2(?)																										404		Bleeding concluded
2:03		29																			61							5.00			
10		29																														
16	100.2			8	40.4	0.4	1.2	12.4	6.63	5.37	.356	385	279	20.65	+17	+6	−2.37	.354		26									409		
18		47																														
39		73																[.659*]	6350											19	Thiocyanate reinjection, 3.8 cc. i.v.
45	100.2	72	1.2(?)																	26	61							3.80		21	Thus far 2 cc. citrate sol. has entered the blood stream
											.334																				
3:00		69		9	39.8	0.7	1.2	11.5	6.46	5.29	[.864*]	376	298	19.92	+11	+27	−2.94	.704											414	24	Reinjection of dye, 3 cc. i.v.
15	100.4	65		10	39.9	0.5	1.6	11.8	6.02	5.41	.854	372	269	20.12	+10	0	−2.58	.653		26									419		
20				11	40.1	0.4	1.5	11.9	5.92	5.09	.830	376	272	19.14	+17	+5	−2.41	.634											424		
25		62		12	40.0	0.5	1.5	11.9	5.85	5.38	.822	373	270	20.10	+17	+5	−2.29	.648			65							3.46	429		
30				13	40.1	0.5	1.4	11.9	5.56	5.47	.819	368	266	20.14	+15	+3	−1.98	.594											434		
42		55	?																		64	17.5	5.0	71.5	0.51	37.0	31.1	3.84	442		
4:19				14	39.7	0.2	1.6	11.7	5.34	5.29	.759	356	252	18.86	+11	−4	−2.85	.673											447		
22		37																			62	14.8	4.2	71.7	0.58	35.5	26.7	4.62	455		
35	100.0			15	38.1		1.4	11.3	5.44	5.26	.759	338	230	17.78	+1	−19	−4.50	.634		26									460		
37		33																														Infusion started, physiological salt sol. i.v.

* Extrapolated values.

TABLE 1—*Concluded*

TIME	TEMP. RECTAL	PRESSURE		SPEC. NO.	CONCENTRATIONS IN BLOOD							VOLUMES			SHIFTS			"AVAILABLE" FLUID		URINE CUMUL. TOTALS	OXYGEN				CARDIAC OUTPUT	CO_2		RESP. VOL.	CUMULATIVE TOTALS		
					Hematocrit																									
		Art.	Ven.		Red	Mixed	White	Hgb.	RBC count	Plas. prot.	Dye	Plasma	Circul. cells	Total protein	Water	RBC	Plasma protein	Thiocyanate	Estimated vol.		O_2 Uptake	A_{O_2}	V_{O_2}	Coeff. utiliz.		Ven.	Art.		Blood removed	Fluid injected	
	°F.	*mm. Hg*	*cm. H_2O*					*gm. %*	*millions*	*gm. %*	*L620*	*cc.*	*cc.*	*gm.*	*cc.*	*cc.*	*gm.*	*L490*	*cc.*	*cc.*	*cc./min.*	*cc. %*	*cc. %*		*l./min.*	*cc. %*	*cc. %*	*l./min.*	*cc.*	*cc.*	
5:01		65	?																	30										
15		65																												
27																													324	Infusion stopped after 300 cc.
32	99.0			16	29.0		1.0	9.3		4.08	.531	435	186	17.75	−199	−61	−3.41	.569		40	74	13.6	6.8	50.0	1.03	40.0	27.4	4.14	468	327	5 cc. citrate has run in altogether
6:09		65	?																		73							4.88			
20																					60							3.17			
26				17	30.9		1.1	10.9	4.76	4.32	.536	379	178	16.37	−246	−65	−4.40	.491		47									473		
38		56																			61							2.93			
7:00	99.2	53																		49										
19		49	?																	51	63							2.68			
35				18	30.7		1.3	9.7	4.34	5.11	.492	358	168	18.28	−264	−73	−2.34	.589			60							2.96	478		
8:07	99.0	46	?																	51										
35				19	30.8		1.2	9.7	4.64	4.97	.472	331	155	16.46	−288	−84	−4.04	.557			56							2.88	483		
55		42																												
9:03																					51							2.31			
24																						14.8	3.2	78.4	0.50	37.9	25.2	2.53	491		Foul, bloody stool—42 gm.
30				20	29.1		0.9	9.0	3.72	4.76	.425	332	142	15.79	−284	−95	−4.64	.668		51	58							2.77	497		
51		43																												
10:18		33																												
31				21	28.4		0.6	8.75	4.65	4.94	.400	309	126	15.28	−297	−107	−4.55	.561		51	51							2.77	502		
11:00	97.9		?																		47							2.07			
30		26		22	28.6		0.8	8.75	5.26	4.90	.374	294	129	14.41	−309	−102	−5.27	.569											507	328	6 cc. citrate has run in altogether
40		10																		51										Respirations ceased
41		8																												Heart stopped

bleeding was continuous rather than intermittent, the effect was usually a progressive fall in blood pressure as shown in figure 7. A constant rate of blood-letting (for example, 6 cc. per minute) produced a more convex curve than the one shown, whereas a rate regulated by venous pressure, a decreasing rate, tended to produce a straight curve. After bleeding was discontinued, the blood pressure remained at its new low level for a while, then declined slowly, and usually terminated with a sudden "break" and a precipitate fall toward zero. The pressures at

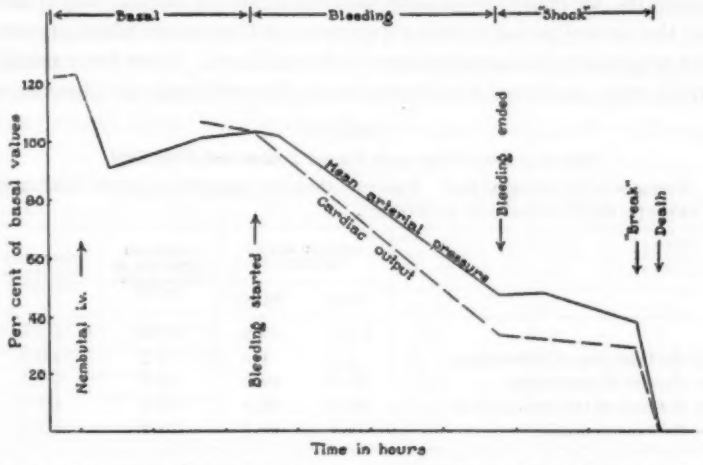

FIG. 7. COMPOSITE CURVES[5] SHOWING THE EFFECTS OF SLOW MASSIVE HEMORRHAGE UPON MEAN ARTERIAL BLOOD PRESSURE AND CARDIAC OUTPUT

The dotted portion of the blood pressure curve was estimated from systolic pressures in the tail.

[5] Because the experiments varied considerably in duration, figures 7, 8, 9, 10 and 12 are necessarily semi-diagrammatic. The curves are drawn from averages of analogous readings of all experiments on a time-scale that is itself a mean. That appears to be a justifiable procedure. Statistical analysis of our blood pressure curves (which, having been recorded continuously, lend themselves to such a study) support an impression received during the experiments, that, except for immediate reactions and adjustments, the effects of acute hemorrhage upon blood pressure are much the same whether blood is removed rapidly or slowly, continuously or intermittently. It is assumed that that is true also for cardiac output, blood concentration, and other aspects which we have studied. To facilitate comparison, most of the curves are drawn on a percentage scale, basal values being 100.

the end of bleeding averaged 63 mm. Hg. (n 32, R 96–30 mm., σ 15 mm.); and at the "break", 47 mm. (n 18, R 66–22 mm., σ 13 mm.).

The cardiac output showed relative changes roughly similar to those of the blood pressure (figure 7). Valid comparison of the two curves, however, depends upon a proper choice of basal values for each. In the case of the blood pressure, which is comparatively stable and is being recorded constantly, such a choice is an easy matter; but the cardiac output varies greatly in the normal dog even under anesthesia. Consequently, we made two or more determinations of cardiac output during the control period of each experiment, at times when blood pressure and respiratory exchange appeared to be stabilized. From these results, which were considered also in relation to the coefficient of utilization of

TABLE 2

Effects of Hemorrhage upon Plasma Volume and Fluid Shift

Averages for 15 untreated dogs. Figures in the upper rows are not altered significantly if values for the 16 treated dogs are included.

	REMOVED DURING EXPERIMENT		OBSERVED REDUCTION IN TOTAL PLASMA VOLUME	FLUID SHIFT INTO PLASMA (NET GAIN)
	Blood	Plasma		
	cc./kg.	*cc./kg.*	*cc./kg.*	*cc./kg.*
By the beginning of hemorrhage	2.5	1.4	1.2	+0.2
By the end of hemorrhage	33.4	19.6	16.5	+3.1
By the time of the break in B.P.	34.0	20.1	16.7	+3.4
By the time of death	34.3	20.3	16.5	+3.8

oxygen and to the average cardiac output for all our normal dogs, a basal rate was estimated for each animal. Average cardiac output in the present series of dogs, in liters per minute per sq. m. of body surface was as follows: basal 3.57 (n 13, R 2.48–5.82, σ 0.95); at the end of bleeding 1.05 (n 12, R 0.61–1.46, σ 0.22); at the "break" 0.91 (n 11, R 0.61–1.18, σ 0.17).

In 8 experiments fairly satisfactory determinations of cardiac output were obtained during the period of rapidly failing circulation after the break in blood pressure. In 4 of these, reduction in cardiac output appeared to be proportional to the fall in mean arterial pressure, as indicated in figure 7; in 2 the decline of blood pressure seemed to be more rapid than the decrease in cardiac output; in 2 the relationship was doubtful.

Venous pressure fell more rapidly than arterial pressure, reaching near-zero values by the end of massive bleeding.

Similarly, volume flow of blood through an extremity was found to be greatly reduced by massive hemorrhage. Subsequently this flow varied a good deal, but on the average remained at about the same low level. It did not cease entirely, however, until death; nor was it observed to increase at or after the break in blood pressure.

Effects of massive hemorrhage upon blood volume and body fluids:— The present series of dogs came to experiment with an average plasma volume of 50.2 cc. per kg. of body weight (n 37, R 41.0–63.6 cc., σ 7.6 cc.). Changes in plasma volume were relatively slight throughout the control period, but the volume of plasma measured by the dye injection method was reduced a great deal by bleeding, as shown in figure 8. Although

TABLE 3

Effects of Hemorrhage upon "Circulating Blood Cell Volume"

	OBSERVED CIRCULATING CELL VOL.	EXPECTED CIRCULATING CELL VOL.	CELL SHIFT (INTO THE BLOOD STREAM)
	cc./kg.	*cc./kg.*	*cc./kg.*
At beginning of experiment	40.6	40.6	0
At beginning of hemorrhage	44.1	39.4	+4.7
At end of hemorrhage	28.3	24.2	+4.1
At break in blood pressure	27.2	23.4	+3.8
At death	26.6	23.1	+3.5

fluid was found to have been added to the plasma from extravascular sources during the period of slow bleeding, the amount was not nearly enough to restore the original plasma volume, as indicated in Table 2. It is noteworthy that so little change in plasma volume occurred in the posthemorrhagic period, even during the final stages of circulatory collapse.

The total volume of circulating blood cells (see previous section for a discussion of this term) increased during the control period, fell during the hemorrhage, and remained nearly constant throughout the post-bleeding period (figure 8). The difference between observed circulating cell volume (deduced from plasma volume and hematocrit value) and expected circulating cell volume (original calculated volume less the amount removed in bleeding and sampling) gives a value which may be

termed the blood cell shift. It indicates that cells have been added to or removed from circulating blood by means other than deliberate bleeding. Table 3 gives a summary of these volumetric studies on the same 15 dogs. The figures in the Table have relative rather than absolute values. None of the animals had been splenectomized. The initial, relatively large shift in circulating blood cell volume is thought to be due partly to reaction after nembutal, and partly to stimuli of operative trauma and blood sampling. In some instances the first few minutes of slow venous bleeding witnessed a further increase in circulating cell volume, the result of a temporary shift of cells from blood depots.

In 12 dogs of the present series, comparative study of plasma volume, "available" body fluids, size of fluid shift, and resistance to bleeding failed to disclose any definite or constant interrelationship. This unexpected negative result is probably attributable to the small number of animals studied and the presence of other variable factors such as breed, age, plasma protein concentration, electrolytes, circulating cell volume, and reserves of various sorts.

Excretion of urine was slowed by severe hemorrhage, ceasing entirely whenever the mean blood pressure reached a level of 60 to 70 mm. Hg. Anuria persisted as long as the blood pressure remained at or below that level; but urine always reappeared promptly when for any reason the pressure rose above it.

Since dogs are almost devoid of sweat glands, and since the animals in this series exhibited no salivation, vomiting, diarrhoea, or abnormal collections of free fluids, loss of water was almost entirely by way of the kidneys and lungs. Insensible loss was estimated to average about 0.6 cc. per kg. per hour under basal conditions. Following hemorrhage the rate of loss was increased somewhat, probably in proportion to the volume of respiratory exchange.

Effects of massive hemorrhage upon concentration and morphology of circulating blood cells:—Control experiments showed that rest is sufficient to reduce the hematocrit readings of active dogs by 6 or 8 points (for example, from 48 to 42). Nembutal reduced them somewhat further. This decrease in cell/plasma ratio was associated with increase in size of the spleen. The postanesthetic fall in hematocrit value was followed by a slow rise (figure 8), which is due partly to reaction after

nembutal and partly to stimuli of operative trauma and blood sampling. The first few minutes of bleeding often produced a further rise in hematocrit owing to the fact that red cell depots were emptied more rapidly than the blood stream was diluted by fluid from the tissues. With progressive bleeding, hematocrit readings declined slowly as a result of the diluting effect of fluid shifts. It should be noted that no sudden change in hematocrit readings occurred at or immediately preceding the final collapse of the circulation.

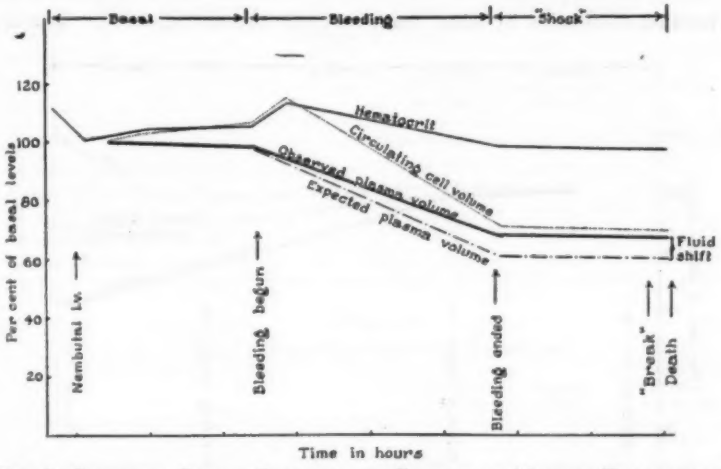

FIG. 8. COMPOSITE CURVES SHOWING THE EFFECTS OF MASSIVE HEMORRHAGE UPON THE VOLUME AND CONCENTRATION OF CIRCULATING BLOOD CELLS, AND THE VOLUME OF PLASMA

Throughout this series of experiments almost identical curves were obtained for hematocrit, hemoglobin, and arterial oxygen content, and the curves of the red cell counts showed fair agreement. The hematocrit curve in figure 8, therefore, serves almost as well for any of the four tests. Such close agreement provides evidence that acute hemorrhage does not within a few hours alter the average size or hemoglobin content of red cells. Furthermore, blood smears from these "shocked" animals showed no appreciable change in size, shape, or color of erythrocytes. Nucleated red cells were rarely encountered.

Leukocytosis occurred in all the experiments and was very irregular. It is impossible to determine from our data how much effect hemorrhage alone had upon the white cell count because of the complicating factors of operative trauma, dye injection which causes a sharp temporary reduction in leukocytes in dogs, and in some cases infection.

Effects of massive hemorrhage upon plasma proteins and nitrogen metabolism:—Protein concentration, averaging 6.14 Gm. per cent (n 34, R 5.00–7.90 Gm., σ 0.75 Gm.) at the outset, as a rule remained unaltered during control periods, but was reduced somewhat following hemorrhage because of dilution by water from the body tissues (figure 9). The ab-

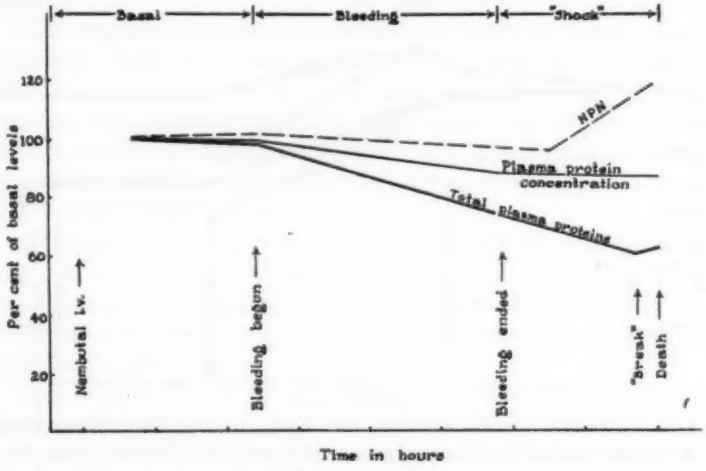

FIG. 9. COMPOSITE CURVES SHOWING THE EFFECTS OF MASSIVE HEMORRHAGE UPON PLASMA PROTEINS AND BLOOD NON-PROTEIN NITROGEN

solute amount of plasma proteins (plasma volume times protein concentration) was reduced, of course, by removal of blood, but otherwise remained almost unchanged, as shown in Table 4. The figures in the last column of the Table, representing quantities of proteins added to or removed from plasma by physiologic or pathologic processes (net gains or losses), are characteristically small in "shock" produced by hemorrhage alone. This observation is important in view of the prevailing theory of increased permeability of capillaries to proteins in shock.

The non-protein nitrogen of the plasma consistently showed a slight rise following severe bleeding. (See figure 9.)

The flow of lymph in the thoracic duct, always small under general anesthetic, was further diminished by hemorrhage until at length it virtually ceased. Hemorrhage was followed by a slight rise in the non-protein nitrogen content of lymph, but not in its protein concentration.

As has been mentioned, bleeding greatly reduced the output of urine. What urine was excreted showed concentration as regards specific gravity and total nitrogen content, but remained free of albumin.

TABLE 4

Effects of Hemorrhage upon Total Intravascular Plasma Proteins

Averages for 16 dogs

	OBSERVED TOTAL PLASMA PROTEINS	EXPECTED TOTAL PLASMA PROTEINS	DIFFERENCE
	Gm./kg. body wt.	*Gm./kg. body wt.*	*Gm./kg. body wt.*
At beginning of experiment	2.99	2.99	0
At beginning of hemorrhage	2.93	2.90	+0.03
At end of hemorrhage	1.84	1.93	−0.09
At break in blood pressure	1.81	1.87	−0.06
At time of death	1.85	1.83	+0.02

TABLE 5

Effects of Hemorrhage upon Blood Electrolytes

	PLASMA CHLORIDES	PLASMA SODIUM	PLASMA POTASSIUM
	m. eq.	*m. eq.*	*m. eq.*
Before hemorrhage	102.9	143.9	6.24
Immediately after hemorrhage	104.9	142.7	5.57
At break in B.P.	105.1	148.9	6.68
At death	105.9	154.9	8.45

In general it may be said, therefore, that relatively minor disturbances of ordinary nitrogen metabolism result from acute massive pemorrhage, and that these disturbances probably played little or no hart in bringing about acute circulatory collapse and death in our animals.

Effects of massive hemorrhage upon blood electrolytes:—The average rise in plasma chlorides and sodium in 4 dogs, and in plasma potassium in 8 dogs is shown in Table 5.

Effects of massive hemorrhage upon respiration:—In dogs especially, the rate of respiration appears to be less important than the minute volume exchange of air. This volume was increased many fold by hemorrhage, an increase which was progressive to the time of death (figures 11 and 12). It was found that this hyperpnea did not increase the oxygen content of the red cells in the arterial blood, nor indeed was it necessary for full re-oxygenation of the blood returning to the lungs; that is to say, the oxygen content of both arterial and venous blood remained almost unaltered if the respiratory exchange of bled dogs was depressed by means of nembutal or morphine. However, hyperpnea did tend to increase consumption of oxygen, probably because of the extramuscular work involved, since no such increase followed excessive artificial respiration. Hyperventilation also accelerated the CO_2 elimination from the lungs and reduced the CO_2 content of venous blood, and there was concomitant lessening of the alkali reserve in the blood.

Since there is no provision in dogs for oxygen storage, save in the hemoglobin, the oxygen uptake through the lungs is an accurate and convenient measure of the total oxygen consumption by the body. In normal animals, oxygen supply is so nicely adjusted to oxygen requirements that the two are equal over any given period of time and oxygen uptake is a true index of oxygen need. Under certain abnormal conditions, however, the supply of oxygen may fail to meet the demands of the body, in which case oxygen uptake measures oxygen utilization but not oxygen need. This latter condition is generally termed anoxia, although it is a matter of deficiency rather than absence of oxygen. A distinction should be drawn between reduction of metabolic rate by rest, narcosis, starvation, cold, and hypothyroidism, and the reduced metabolic rate associated with anoxia. The former conditions exemplify adaptations of the oxygen intake to a lowered oxygen need, whereas anoxia is an acutely dangerous condition in which the oxygen supply falls below the body requirements.

Under "basal" conditions of nembutal anesthesia, oxygen uptake in 74 apparently healthy dogs of different sizes and breeds showed a striking lack of uniformity. The average uptake for the group was 6.49 cc. per minute per kg. of body weight (n 74, R 5.05–11.75 cc., σ 1.75 cc.). In anesthetized, unshocked animals it was found that the oxygen consumption could be raised considerably above the basal rate by means of

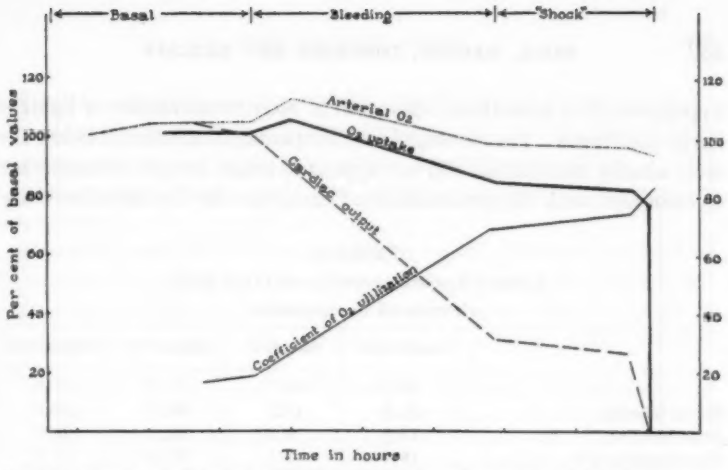

FIG. 10. COMPOSITE CURVES SHOWING THE EFFECTS OF MASSIVE HEMORRHAGE UPON OXYGENATION

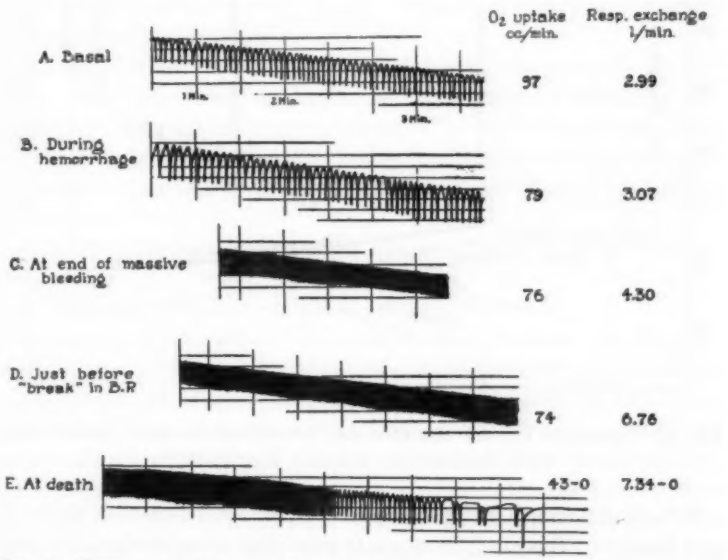

FIG. 11. EFFECTS OF MASSIVE HEMORRHAGE UPON OXYGEN CONSUMPTION AND MINUTE VOLUME OF RESPIRATORY EXCHANGE

These tracings were taken on a metabolism tester, and show that oxygen uptake (indicated by steepness of slope) decreased, whereas respiratory volume increased almost to the time of death.

hyperpnea (CO_2 inhalation), elevation of body temperature, or lightening of anesthesia. On the other hand, deepening of anesthesia below the level usually maintained, did not appear to lessen oxygen consumption as compared with the pre-established basal rate for the individual dog.

TABLE 6

Effects of Hemorrhage upon O_2 and CO_2 of Blood

Average of 15 experiments

	ARTERIAL O_2	VENOUS O_2	VENOUS CO_2	ARTERIAL CO_2
	vol. %	vol. %	vol. %	vol. %
Before bleeding	21.0	17.2	40.5	36.6
After bleeding	18.9	6.8	31.6	20.9
Near break in B.P.	18.4	5.1	28.8	17.1

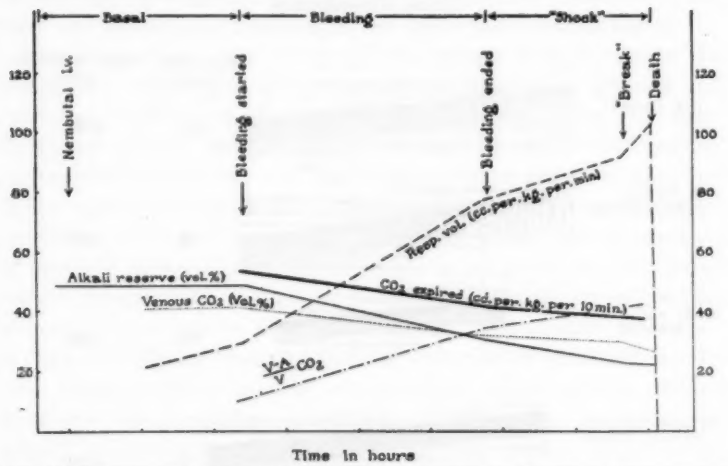

FIG. 12. COMPOSITE CURVES SHOWING THE EFFECTS OF MASSIVE HEMORRHAGE UPON RESPIRATION AND CO_2 ELIMINATION

Effects of hemorrhage upon oxygen uptake are indicated in figure 10 and Table 6. There is little reason to think that after bleeding, the need for oxygen decreased in these animals. On the contrary, it is likely that oxygen requirements were raised above the original basal level because of the extra muscular activity associated with hyperpnea and tachy-

cardia. A decreasing oxygen uptake together with unchanged or increased oxygen requirements during the latter half of these experiments indicates anoxia of mounting severity. A progressive anoxia of this sort was a characteristic feature of all our experiments with massive hemorrhage.

The minute volume elimination of CO_2 by the lungs was reduced in these experiments (figure 12). Respiratory quotient was as follows: just before bleeding 1.02, after bleeding 0.86, at or near the break in blood pressure 0.85. The proportion of venous CO_2 exhaled $\left(\frac{V_{CO_2} - A_{CO_2}}{V_{CO_2}}\right)$, which may be termed the coefficient of elimination of CO_2, rose as the experiments progressed.

Other effects of massive hemorrhage:—Severe bleeding appeared to deepen narcosis. Once bleeding had been started, many of the dogs needed no further reinforcing injections of nembutal, even in cases where death was delayed for several hours. Conversely, successful therapy seemed to waken the dogs.

The heart rate in our animals showed various responses to hemorrhage. The most common finding was a moderate tachycardia, especially if the initial bleeding was rapid. The heart always continued to beat for a minute or two after regular respiration ceased, the pulse at the same time changing from a rapid, weak impulse to a slow, more forceful one.

In most of the experiments there was no significant change in body temperature.

Reduction in clotting time was usually observed.

Postmortem examination:—As far as we could observe, the moment of death was not associated with any sudden anatomical change which might throw light upon the causative mechanism of death; there was no rapid vasodilation, nor appreciable alteration in size of the spleen, nor apparent change in degree of wetness of tissues. All of the animals dying of hemorrhage without therapy showed generalized pallor of tissues and organs. The subcutaneous tissues were moderately dry. No abnormal collections of fluid were found in serous cavities. There was no splanchnic congestion. In the gastro-intestinal tract, subserous and submucous hemorrhages, bleeding into the lumen, and mesenteric hemorrhages were occasionally observed in animals which had received

no therapy. The spleen appeared small and contracted but contained thick blood. The liver was soft and showed little or no congestion, and its cut surfaces bled less than usual. In almost every instance tiny, flamelike hemorrhages, confirmed by microscopic section, were observed in the adrenal cortex. The large venous trunks contained less blood than ordinarily; in some cases they were almost empty. Inconstant observations included subendocardial hemorrhages, and evidence of damage to the central cells of the liver lobules as shown by poor staining and vacuolization. The lungs were oligemic but otherwise normal. The central nervous tissues showed no abnormalities.

DISCUSSION

In the past a number of attempts have been made to correlate initiating, accompanying, and perpetuating factors in shock. Physiologic patterns, showing successive steps in the mechanism of shock, have been suggested by Blalock (3, 31), Freeman (32), Moon (4), McDowell (33), and others. In order to explain satisfactorily the numerous physiologic and pathologic changes observed in shock, many writers have postulated the occurrence also of tissue anoxemia, premortal vasodilatation, capillary atony, "stasis," and abnormal capillary permeability, and have considered them important and characteristic features of shock. These phenomena, however, are not readily demonstrated. That they are plausible answers to the problem of interpretation should not obscure the fact that they are assumptions for which evidence is, at best, indirect. It is important, therefore, to examine the evidence for and against these phenomena in the particular type of shock which we are studying.

Anoxia in a part, or in the body generally, is not easily demonstrated or measured. Arterial oxygen content and cardiac output are not dependable criteria, nor can low venous oxygen content or tension be used as an index of anoxia since more efficient reduction of blood is itself one of the compensatory adjustments which help to maintain adequate supply of oxygen to tissues. A fall in the total oxygen consumption to a point well below the predetermined basal rate may be considered presumptive evidence of oxygen want, but it does not constitute proof since present methods do not permit measurement of bodily requirements of oxygen under conditions of shock. Furthermore, because of selective blood flow, certain regions may receive adequate amounts of oxygen at

the expense of other regions. And finally, different tissues vary tremendously in sensitiveness to oxygen lack. Reviewing our experimental data in the light of these considerations we have concluded (1) that progressively severe anoxia probably always occurs as a result of massive hemorrhage, and (2) that vital centers and organs do not appear to share in this general oxygen lack at first, though they probably do later.

Large-scale vasodilatation, or rather, relaxation of vasoconstriction, obviously did not occur in our animals. No congestion was noted in the splanchnic region or elsewhere. The large veins appeared nearly empty before and after death. The blood flow through the extremities did not increase during the final stage of circulatory failure. Cardiac output and blood pressure showed a tendency to diminish in like proportions throughout the period of shock. These observations do not exclude the possibility, however, of a very slight but important degree of vasodilatation just before death. In the late stages of posthemorrhagic shock, dogs become extremely sensitive to blood loss, so that removal of even a few cubic centimeters may precipitate collapse of the circulation. It is conceivable that, on the same principle, an imperceptibly small, general vasodilatation might upset an already precarious balance between blood volume and vascular bed capacity.

No direct or indirect evidence of capillary atony or "stasis" (engorgement of capillaries with local hemoconcentration from loss of water into tissues) could be found in our bled dogs. Nor was there any indication that the capillaries became abnormally permeable to water, proteins, whole plasma, or blood cells. Our studies have led us, rather, to the conclusion that simple acute hemorrhage does not result in "leaky" capillaries. During the "shock" period, up to the time of death, there were no sudden reductions in plasma volume (figure 8, Table 2), no suggestive concentrations of plasma proteins (figure 9) or blood cells (figure 8), and no unaccountable loss of total plasma protein (figure 9, Table 4). Furthermore, the dye T-1824, which combines with plasma protein, was found to "disappear" from the blood at the same rate after hemorrhage as before, which was not the case in other types of shock (35) where capillaries were traumatized locally, permitting demonstrable leakage of serum or blood into the tissues. A crucial experiment was to inject very large amounts of this dye into the veins of a number of dogs

not in the present series, a procedure which enabled us to observe directly abnormal leakage of dye, and presumably protein, into the tissues. Although local staining of tissues was pronounced in areas subjected to trauma of different sorts, no abnormal staining of tissues in general was observed in animals dying of posthemorrhagic shock. The idea of increased capillary permeability has been advanced also to explain the failure of injected fluids (saline, serum, or whole blood) to remain quantitatively in the vascular beds of shocked animals. That contention is weakened, however, by the discovery that even larger proportions of such infusions leave the blood stream when they are injected into normal animals.

Assuming, therefore, that anoxia developed in our animals but that atony, "stasis," and abnormal permeability of capillaries did not occur, we shall attempt to interpret our observations and to trace the course of events leading from hemorrhage to circulatory collapse and death.

A. *Primary effects of acute blood loss:* These are hemodynamic,—diminished blood volume, decreased flow of blood through the heart and through body tissues, reduced arterial and venous blood pressure. Fundamentally these are purely physical effects which can be reproduced in a mechanical circulation model by simply removing some of its circulating fluid (35), although in the animal they are modified by physiologic adaptations which will be discussed under heading C.

B. *Secondary effects of acute blood loss:* Reduction of blood volume and slowing of its circulation, if not compensated for, inevitably disturb the ordinary vital functions of blood. One function of blood is to provide continuous adequate supplies of oxygen to all the tissues, especially to those of vital organs. Without oxygen, these organs immediately cease to perform properly, and soon fail completely. Other vital processes, such as elimination of CO_2 and other products of metabolism, regulation of body temperature and water balance, nutrition, and hormonal activity, are likewise absolutely dependent upon efficient blood circulation. It might be expected, therefore, that posthemorrhagic depression of the circulation would be followed by a great variety of functional and organic abnormalities. Actually, few are found. The reason, perhaps, is that oxygenation is the function of blood most promptly and seriously disturbed by massive hemorrhage, and animals succumb from anoxia before other pathologic changes have had time to develop.

A number of our experimental results can be explained on this basis. The apparent deepening of narcosis following hemorrhage was probably an indication of reduced oxygen supply to the cerebral cortex. Premortal slowing of the heart beat and sudden cessation of respiration (figure 11) were almost certainly due to anoxia in the bulbar nervous centers. The sudden collapse of the circulation which terminated periods of "shock" was very likely a result of anoxia also; but whether this collapse was effected through vasodilation, enfeeblement of the heart beat, or some other mechanism we do not know. An increase in the lactic acid in the blood following hemorrhage, reported by many observers, and lowering of alkali reserves were evidences of incomplete oxidation, in muscles especially. Histologic changes noted in liver cells, hemorrhages in the adrenal cortex, and rise in electrolytes were also secondary effects of hemorrhage, but the significance of these changes is not clear.

Secondary pathologic results of massive hemorrhage, though vaguely manifested, are of utmost importance. In untreated animals they are apt to be progressive and fatal. It is reasonable to suppose that anoxia, a result of impaired blood supply, may reciprocally depress the circulation further; and this vicious circle, if not broken, may lead quickly to death.

To what extent these pathologic effects of hemorrhage should be considered "irreversible changes" is a moot point. Since dead animals cannot be revived, such changes undoubtedly have occurred in them. On the other hand, some of our severely bled dogs, which were given whole blood transfusions after extended periods of anoxia, even after the final break in blood pressure, were checked in their downhill course and eventually recovered completely. In these animals, apparently, posthemorrhagic shock progressed to a point where death seemed imminent, without the development of irreversible, in the sense of irreparable, organic changes.

C. *Compensatory physiologic adjustments:* The pathologic effects just described do not ordinarily appear after small or moderate sized hemorrhages, and in any case are lessened and delayed owing to the action of a number of compensatory mechanisms.

First, the heart beats somewhat more rapidly and forcefully, tending to improve cardiac output and maintain arterial blood pressure. This

reaction occurs promptly after bleeding begins. It probably loses much of its effectiveness as soon as the blood volume is reduced to an extent that interferes with the filling of the heart during diastole.

Second, vasoconstriction occurs, particularly in skin, subcutaneous tissues, and skeletal muscles, but also in certain parenchymatous organs such as the salivary glands (Gesell (34)) and kidneys. This selective vasoconstriction reduces the size of the functioning vascular bed, and in consequence the depleted volume of blood becomes less inadequate for essential purposes. Since the blood vessels supplying the heart and central nervous system probably do not share in the general vasoconstriction, blood is diverted to these vital organs, so that for a time their usual circulation may be maintained. Vasoconstriction also lessens heat loss from the body, and conserves body fluids by reducing the excretion of saliva and urine. This vasomotor response to hemorrhage is also early, becoming more pronounced as bleeding continues. In acute experiments it appears to persist until death.

Third, shifts of fluid (water and diffusates) from tissues, and of blood cells from depots help to make up for the reduced volume of circulating blood and the deficient supply of circulating hemoglobin. Transfer of fluids begins almost at once and is most active during bleeding. In case of severe blood loss, this fluid shift may fall far short of maintaining the original plasma volume (figure 8). Blood cell reservoirs, such as the spleen, are partly emptied with the onset of bleeding, but in untreated dogs show little change thereafter.

Fourth, dissociation of oxyhemoglobin in peripheral capillaries is increased, so that instead of releasing the usual one fifth of its load of oxygen, blood now gives up three fifths or four fifths, yet is fully recharged with oxygen on each return trip to the lungs. This important compensatory mechanism, which may be attributed in part to lowered oxygen tension in the tissues, and in part to chemical changes in the blood which favor dissociation of oxyhemoglobin, gets under way slowly, and reaches maximal effectiveness as oxygen lack in the body as a whole becomes pronounced (figure 10).

Fifth, hyperventilation develops progressively. This facilitates oxygenation of both blood and tissues through a complex set of physicochemical adjustments, but at the same time the extra muscular work adds to existing oxygen needs. Hyperventilation also assists in elimina-

tion of CO_2, so that despite impaired transport due to reduced bicarbonate and slow circulation the amount of CO_2 in arterial and venous blood and in tissues is not seriously altered (Table 6). Hyperpnea undoubtedly increases insensible loss of water.

By means of these compensatory mechanisms the normal animal is well fortified against oxygen lack or excessive accumulation of CO_2. This margin of safety is narrowed by blood loss. If hemorrhage is very severe, the mechanisms at length fail to compensate fully. When this happens spontaneous recovery is unlikely. In our untreated animals a persistent anoxia of several hours' duration was always followed by circulatory collapse and death.

D. *Regeneration of blood:* This response to hemorrhage is well known. Restoration of water begins immediately, but if much blood has been lost, plasma volume may not return to normal for 24 or more hours. Replacement of lost plasma proteins begins soon after hemorrhage. Elevation of the blood non-protein nitrogen is thought by some to indicate mobilization of body proteins to that end. Reduction in clotting time is probably evidence of rapid production of fibrinogen. By the end of 48 hours the total amount of plasma proteins in a healthy dog may be greater than it was before the hemorrhage. Regeneration of erythrocytes and of hemoglobin are much slower processes, of course. On the whole, restoration of blood by natural means is a relatively slow process which in our acute experiments was overtaken near the start by death of the animals.

In brief, the primary effect of acute hemorrhage is a direct disturbance of hemodynamics. The resultant circulatory depression affects the body secondarily by interfering with the functions of the blood, especially that of tissue oxygenation. These primary and secondary effects of blood loss are compensated for by physiologic adjustments, but progressively less adequately until decompensation occurs, with resultant anoxia of vital centers. Regeneration of blood is too slow to be of much help here. Failure of vital organs causes further circulatory depression, and this vicious circle leads ultimately to stoppage of the circulation, irreparable organic damage, and death.

This concept accounts satisfactorily, we believe, for nearly all of our experimental observations. It is supported by experiments in which we bled dogs sublethal amounts. In these animals the decompensation just

described appeared only transiently, or not at all, and regeneration of blood led to full spontaneous recovery. Further corroboration is provided by the group of experiments in which death from massive hemorrhage was averted by therapeutic measures. In these animals it was possible to observe sustained improvement in circulation and permanent restoration of adequate oxygenation.

Finally, this particular pattern of physiologic and pathologic effects is characteristic of acute hemorrhage. As will be shown in subsequent papers, it is not reproduced when shock is brought on by other methods.

SUMMARY

As part of a systematic study of experimental shock, the effects of acute hemorrhage upon 37 healthy, anesthetized dogs have been observed. Critical care was exercised in selection and use of technical methods. Each animal was studied intensively both before and after bleeding. Results of these experiments are presented.

An attempt is made, moreover, to integrate our experimental results so as to obtain a unified picture of the progressive response of the animal to blood loss. To this end the effects of hemorrhage are divided into four groups: (1) primary dynamic effects, (2) secondary pathologic effects, (3) physiologic compensatory protective mechanisms, and (4) regeneration of blood elements.

The circulatory depression which follows blood loss is fundamentally a matter of hemodynamics. Its ill effects may be averted or lessened through the operation of a number of compensatory physiologic adaptations. When these fail, a progressively severe anoxia occurs, followed by secondary pathologic effects. Without therapy, collapse and death inevitably ensue.

Evidence is presented to show that capillary atony, "stasis," and abnormal permeability of capillaries probably do not occur in dogs following uncomplicated acute hemorrhage.

The effects of acute massive blood loss, taken together, are sufficiently characteristic to constitute a distinctive type of experimental shock.

We received valuable assistance from Drs. Herbert E. Sloan and Burt H. Christensen in carrying out some of the experiments; from Dr. Frank J. Otenasek in pathological studies; and from Dr. Marie Cakrtova of the Department of Biostatistics, School of Hygiene, in a statistical study of the relation of bleeding rate to blood pressure fall.

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RESULTS OF ARTIFICIAL PNEUMOTHORAX THERAPY IN PULMONARY TUBERCULOSIS[1]

HUGH G. WHITEHEAD, M.D.

From the Department of Medicine, The Johns Hopkins Hospital, and the Pneumothorax Clinic (Broadway), of the Baltimore City Health Department

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The true value of collapse therapy in the treatment of pulmonary tuberculosis is not reflected in bare statistical studies. These have adequately proved the efficacy of the method, but it is difficult to evaluate properly by tabulations the many factors which influence the final results. The more important of these factors are outlined in Table I.

I. *Dominant tissue reaction.* This factor has been accorded first consideration in most reports evaluating the results of collapse therapy. It was particularly stressed in a review of 530 cases by Aycock and Keller (1), in 1938. Their percentage of satisfactory results in the exudative group alone was 73.5 and they point out that lesions in the exudative group are, in reality, in the exudative *phase* which is more or less transitory. They conclude that the high percentage of good results from artificial pneumothorax in cases of this group means that this is the optimum phase in which to apply this form of therapy.

II. *Extent of lesion.* The great importance of this factor is self-evident. The pronounced tendency of the minimal lesion to heal on rest alone, and the high incidence of important complications in the fibrocavernous types of lesions naturally determine end results.

III. *Type of collapse obtained.* The extent of pulmonary collapse and the presence or absence of adhesions are of less importance than closure of a cavity and a persistently negative sputum in determining the efficiency of an artificial pneumothorax. The degree of pulmonary involvement and the character of the lesion primarily determine the optimum duration of collapse therapy. Of necessity social and eco-

[1] Presented in part at a meeting of the Johns Hopkins Medical Society, May 13, 1940.

nomic factors must also be considered in this regard; not infrequently the ultimate outcome is favorable in spite of the fact that the treatment is abandoned by the patient against the advice of the physician.

IV. *Status of opposite lung.* The satisfactory results obtained by the induction of bilateral simultaneous artificial pneumothorax by Tice and Hruby (2), Carman (3), Corsello (4), and others, have made a consideration of the contralateral lung of less importance in recent years. In any case it is desirable to observe the course of the disease

TABLE I

Factors Influencing the Results in Artificial Pneumothorax Therapy in the Treatment of Pulmonary Tuberculosis

I. Dominant tissue reaction A. Exudative (caseous pneumonic) B. Proliferative (fibrocavernous) C. Mixed	II. Extent of lesion A. Minimal B. Moderately advanced C. Far-advanced
III. Type of collapse obtained A. Efficient (sputum negative, cavity closed) B. Inefficient (sputum positive, cavity open) C. Duration	IV. Status of opposite lung A. Type of involvement B. Extent of involvement
V. Clinical picture A. Tendency to heal on rest alone prior to collapse therapy B. Fever, tachycardia, weight loss C. Sedimentation rate and leucocytic index D. Age, sex and race	VI. Type of patient A. Intelligence and cooperation B. Social-economic factors (opportunities for rest and adequate diet) C. Care after reexpansion (activities, pregnancies, regular observation by physician)

until the patient's condition is stabilized, but an active and even an extensive process in the opposite lung is no contraindication to the establishment of a therapeutic pneumothorax. It may be quite apparent at the beginning that bilateral simultaneous collapse will be necessary. While the status of the opposite lung is a minor consideration in deciding upon the advisability of collapse therapy, it is a factor that plays a tremendous part in determining end results.

V. *Clinical picture.* The well-known tendency of pulmonary tuberculosis to heal spontaneously with rest alone, sometimes without

rest, makes a period of observation prior to considering collapse therapy most desirable, provided there are no indications, such as repeated hemoptysis, for immediate collapse therapy. If there is a pronounced tendency toward resolution of a lesion prior to therapeutic collapse then a favorable outcome in such a case cannot be attributed wholly to the artificial pneumothorax. Since many cases have a pneumothorax which is induced without this period of observation, and all too frequently when the lesion under consideration is not proved to be tuberculous, this factor can seldom be properly evaluated in an analysis of end results in collapse therapy.

VI. *Type of patient.* Perhaps no single factor contributes more to the success of collapse therapy than the cooperation of the patient. This is self-evident when one realizes that the optimum duration of the procedure, in most cases, is measured in years. Accordingly, the general intelligence of the patient, his emotional stability and grasp of what is explained to him about the proposed procedures, are indices of his confidence in his medical advisors, upon which depends his cooperation over a period of years. It is certainly desirable to explain at the outset exactly what is to be undertaken and for how long; and the patient's willingness to cooperate, based on his full understanding of what lies ahead, must be taken into account. Social and economic factors which may or may not permit adequate rest and diet, greatly influence the outcome of collapse therapy; and proper care and periodic checkup, both during treatment and after re-expansion of the lung takes place, play a large part in determining results. All this is not idle speculation: each factor is a practical consideration in the proper management of the patient. It is a common experience in pneumothorax clinics to encounter patients who have no idea of what is being done for them, no conception of how long it is going to take, and no appreciation of the importance of regular attendance. Under these circumstances, the regular refills become burdensome, the patient's confidence is lost, he "shops" around, receiving conflicting advice, and the end result is loss of effective collapse, pleural effusion or empyema; and another failure is charged against collapse therapy.

With these factors in mind, the results of collapse therapy reported in 15 outstanding articles since 1924 can be more intelligently analyzed. Composite percentage results of these reports are shown in

Table II. It may be seen that about two thirds of those with efficient collapse are "living" (after a variable period of years) whereas less than one third with inefficient collapse progress favorably. Although "living" does not necessarily denote successful control of the disease, it is safe to say that the great majority of those with efficient collapse resume activity approaching normal, and many are self-supporting. Chart 1 demonstrates graphically the comparison of results obtained

TABLE II

Composite Percentage Results of Fifteen Reports on Results of Artificial Pneumothorax Therapy in Pulmonary Tuberculosis Since 1924

	DATE OF REPORT	AUTHOR	EFFICIENT COLLAPSE	LIVING	INEFFICIENT COLLAPSE	LIVING	TOTAL
				per cent		*per cent*	
1	1924	Matson et al.	235	66	245	23	480
2	1925	Gravesen	143	38.5	73	11.8	216
3	1927	Rist	759	69.5	94	45.7	853
4	1928	Kendall	143	63.7	82	33	225
5	1929	Cooper	104	52	78	22	182
6	1929	Peters, L., et al.	167	53	140	25	307
7	1930	Amberson	89	87.6	76	41.6	165
8	1930	Peters, A., et al.	151	94	245	59.6	396
9	1932	Macfie	166	57	34	38	200
10	1933	Ahlenstiel	136	51.4	166	25.4	302
11	1933	Burrell	153	34	29	14	182
12	1936	Bentley	208	65.9	267	50	475
13	1937	Leslie	595	77.8			595
14	1938	Aycock	301	57	229	20	530
15	1939	Tice and Hruby	3090	69.3	337	33	3427
Grand totals			6440		2095		8535
Average				63.7		30.4	

in efficient and in inefficient types of artificial pneumothorax. The importance of securing, at an early date, an *effective* collapse cannot be stressed too often, and in this the close cooperation of specially trained thoracic surgeons plays a major part. Individuals with strictly unilateral disease, in whom a *complete* or *effective* collapse has been obtained, have so far formed less than one quarter of the reported cases. *Incomplete* or *ineffective* artificial pneumothorax, reported in 60 per cent of the cases reduces the general level of successful results.

REVIEW OF THE JOHNS HOPKINS HOSPITAL CASES

Since 1930, 172 patients have been treated in the Pneumothorax Clinic of the Johns Hopkins Hospital. The statistical details of this small group are of little significance. The majority were white, and females exceeded males. The youngest was 7 years of age, and the oldest 58 years; the average age for the group was 25 years. Chart 2 shows briefly the present status of the group. As far as could be determined, the lesions in all of the cases were moderately or far-

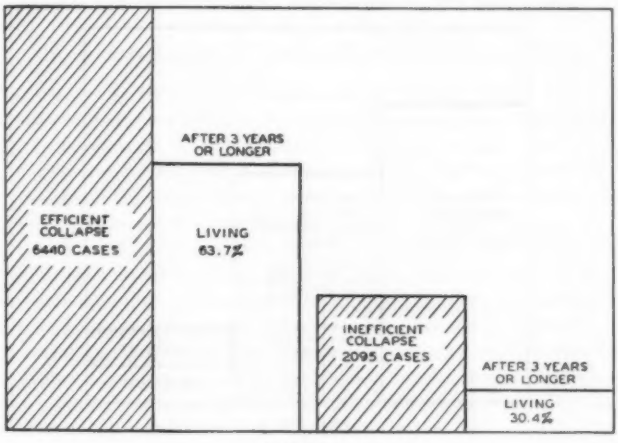

CHART 1

Comparison of Results Obtained in Efficient and Inefficient Types of Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis

advanced when therapeutic pneumothorax was commenced. The percentage of successful results to date is above the average. It is true, perhaps, that only the most favorable cases come to us from the sanatoria and hospitals, but this advantage is somewhat offset by the fact that all of the dispensary patients are *ambulatory*. Many of them work for their living or do an average amount of housework, and only a very few combine their collapse therapy with systematic and conscientious rest periods.

Of the 123 individuals (77 per cent living and still under observa-

tion), this report is chiefly concerned with 69 (40 per cent) whose lungs have been reexpanded, and who now show no evidence of active disease. In 64 (37 per cent) of the group, still receiving refills, the ultimate results are still uncertain.

The following cases are reported in some detail, and with serial x-ray films, as examples of representative end-results, as well as demonstrations of complications that may arise during the course of pneumothorax therapy. The efficacy of collapse therapy of relatively short duration is also illustrated.

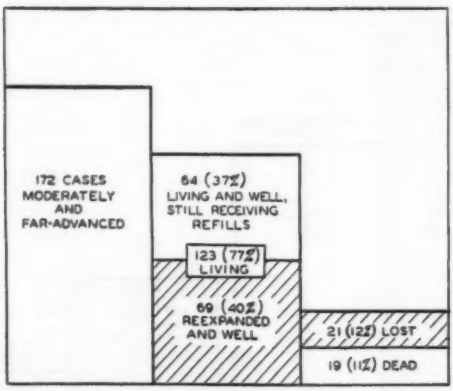

CHART 2

Results in 172 Cases of Pulmonary Tuberculosis Treated with Artificial Pneumothorax in the Johns Hopkins Hospital Dispensary, 1930–40

I. Duration of collapse therapy over 5 years

Figure 1 illustrates prolonged artificial pneumothorax, with almost complete clearing of the lung and hardly perceptible mediastinal dislocation after reexpansion.

Figure 2 demonstrates a reexpansion after 5 years of collapse, with fluid formation and considerable residual fibrosis and shift.

Figure 3 shows dense obliteration and mediastinal shift after 5 years of artificial pneumothorax, but a clinically inactive lesion.

Figure 4 shows elevation of right diaphragm and fibrotic residual in lung, but little mediastinal shift, after 5 years therapeutic pneumothorax.

Figure 5 illustrates the amount of fibrosis and mediastinal shift which might be expected after 3 years of comparatively extensive collapse of left lung.

II. Value of artificial pneumothorax of short duration and small in extent

Figure 6. A therapeutic pneumothorax of relatively short duration, mostly limited to the base, but quite effective in healing an apical and midzone lesion.

Figure 7 shows remarkable clearing after 9 months collapse for a caseocavernous left upper lobe lesion in a 52-year-old colored female.

Figure 8. Artificial pneumothorax of one year's duration in a young white female with caseocavernous lesion of right upper lobe. Obliteration made it necessary to abandon collapse before complete healing had taken place.

III. Complications of artificial pneumothorax therapy

a. Contralateral spread: bilateral pneumothorax. Figures 9–10. Serial films of a young colored male over a four year period, showing spread to contralateral side, bilateral pneumothorax. Poor cooperation and refusal to rest. End result after 4 years is far-advanced bilateral involvement. Collapse therapy gave him a false sense of security. He should never have been selected for artificial pneumothorax.

b. Secondary tuberculosis of the bronchus; persistent pleural effusion: oleothorax. Figures 11–13. Effective pneumothorax for right lower lobe tuberculosis in a young white male, onset in 1936. Sputum became positive on culture in 1938, with no focus apparent in the parenchyma. On bronchoscopic examination an extensive tuberculous lesion of the right lower lobe bronchus was found. Pleural effusion, which appeared in 1937, persisted and oleothorax was established on the right. Cauterization brought about improvement in the bronchial lesion, and by 1940 the patient was working full-time; tuberculosis clinically inactive, and sputum persistently bacilli free.

One of the most difficult problems in the management of a group of patients receiving collapse therapy is that of periodic examination and follow-up. To abbreviate the records, which become voluminous through the years, and to facilitate the system of follow-up, the cards shown (front and back) in Table III were devised. At a glance the physician giving a refill or making a periodic examination may scrutinize the pertinent facts of the case, and bring the record up to date. Such an abstract of the case record is invaluable in making a critical analysis of a group of patients, and is of great aid in securing the cooperation of social workers in locating patients with whom contact has been lost.

TABLE III

Abstract Card (Front and Back) Used in Following Cases Attending the Pneumothorax Clinic

PNEUMOTHORAX CLINIC

THE JOHNS HOPKINS HOSPITAL, BALTIMORE, MARYLAND

1. Name — Case history no.
2. Address
3. Occupation — Age — Sex — Color — Marital — Birthplace
4. Family history
5. Past history
6. Date of onset, pulmonary tuberculosis:
   Location: name of doctor or institution making diagnosis:
   X-ray, onset:
   N.T.A. classification: — Result of sputum tests:
7. Location, first treatment:
8. Doctor or institution giving first artificial pneumothorax:

Duration of collapse therapy:	1st 6 mos.	2nd 6 mos.	2 yrs.	3 yrs.	4 yrs.	5 yrs.
9. Degree of collapse Average refill, and interval:						

(over)

10. Date of first negative sputum:
    Duration, initial to first negative sputum:
11. Tuberculin tests:
12. Gain or loss of weight:
13. Duration of bed rest:
14. Tuberculous complication:
15. Non-tuberculous complications:
16. Follow-up record:

DISCUSSION

There is no doubt among those with experience in artificial pneumothorax therapy that the results being obtained by the procedure deserve constant and repeated analysis. The foregoing report was designed as a contribution to this need, based on a study of a small group of cases. The long duration of the treatment and the tendency of the patients to migrate make a critical analysis of any large group of cases an extremely difficult undertaking. It is quite clear that statistics alone do not suffice to define the results of collapse therapy. For that reason the most pertinent variables influencing the ultimate outcome have been pointed out in the foregoing report. Serial films of representative cases are illustrated to show what might be expected in a fair proportion of patients to whom therapeutic pneumothorax is administered. Some invariable complications in the procedure are also illustrated. Contralateral spread, the use of phrenic crush, thoracoplasty or further surgery in conjunction with pneumothorax, complicating tuberculous infection of the pleura, upper respiratory passages or elsewhere, and bronchiectasis or thoracic deformity after reexpansion of the lung are all events well-known to phthisiotherapists; but fortunately they seldom occur, considering the great number of individuals receiving pneumothorax therapy.

In a recent report, Bloch, Tucker and Adams (18) have considered some statistics relating to artificial pneumothorax and have emphasized the importance of many of the factors referred to in this report. They particularly stress what must have impressed everyone who has made a critical study of this form of therapy, namely, that the indications for its use need sharper definition, and that its results must be judged by more rigid standards.

In evaluating the results obtained in any given case, after reexpansion of the lung, the question often arises "What would have been the outcome with sanatorium treatment alone?" Many statistical reports in the last decade have attempted to answer this query. Although eight years have passed since its publication, the report of Shaw (19) which appeared in 1933 is perhaps as valuable as any of the larger reports which have appeared since, in giving an indication of the relative mortalities observed in collapse and non-collapse groups, with due

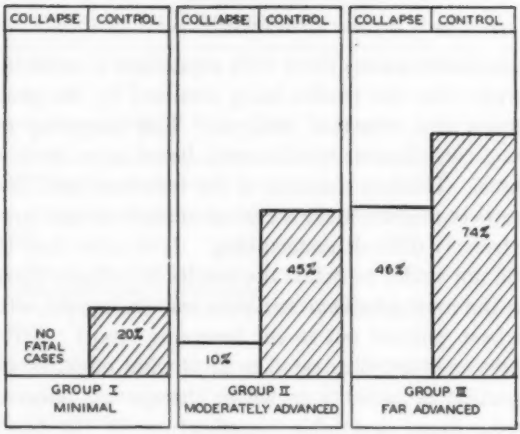

CHART 3

Mortality in 267 Cases of Artificial Pneumothorax in Various Types of Pulmonary Tuberculosis Compared with Control Groups with Sanatoria Rest Only

Shaw: Quarterly Review of Medicine, 1933.

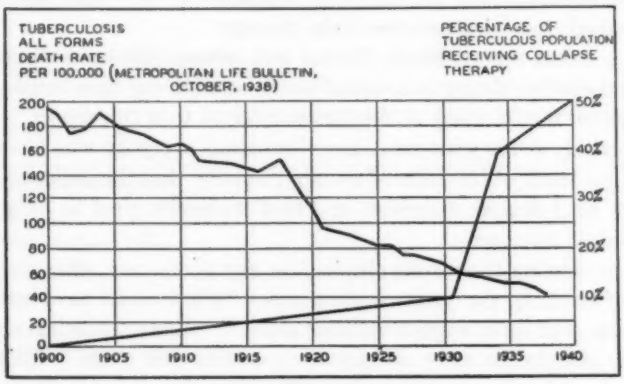

CHART 4

Curve Showing Increasing Use of Collapse Therapy in Pulmonary Tuberculosis Compared with Death Rate per 100,000 from 1900 to 1940

regard for the type and extent of the lesions. Chart 3 is based on Shaw's report.

Perhaps the most persuasive evidence that pneumothorax therapy in pulmonary tuberculosis is an overwhelming success is the tremendous increase in its use since 1930. Although no complete statistics are available, information obtained from the chief statistician of the National Tuberculosis Association in 1940 (20) indicates that about 10 per cent of the tuberculous population were receiving artificial pneumothorax in 1931, about 41 per cent in 1935 and about 50 per cent in 1940. Without implying that there is any relationship between the two curves, the increase in the use of therapeutic pneumothorax since 1900 is plotted in Chart 4, with the general mortality rate for all forms of tuberculosis.

SUMMARY

The dominant tissue reaction, the extent of the lesion, the type of collapse obtained, the status of the opposite lung, the general clinical picture prior to collapse and the type of patient are the most important factors in determining the results obtained by artificial pneumothorax in the treatment of pulmonary tuberculosis.

In general, based on the combined reports of over fifteen investigators since 1924, it might be said that those individuals with an efficient collapse do twice as well as those in whom an effective collapse, judged by sputum conversion and cavity closure, cannot be obtained.

An analysis is presented of the results obtained in 172 cases of pulmonary tuberculosis treated with artificial pneumothorax in the Johns Hopkins Hospital Dispensary between 1930 and 1940.

While statistical studies have indicated the efficacy of artificial pneumothorax as a therapeutic procedure in selected cases of pulmonary tuberculosis, the best evidence of the success of the method is its present widespread use, and the constant increase in its application.

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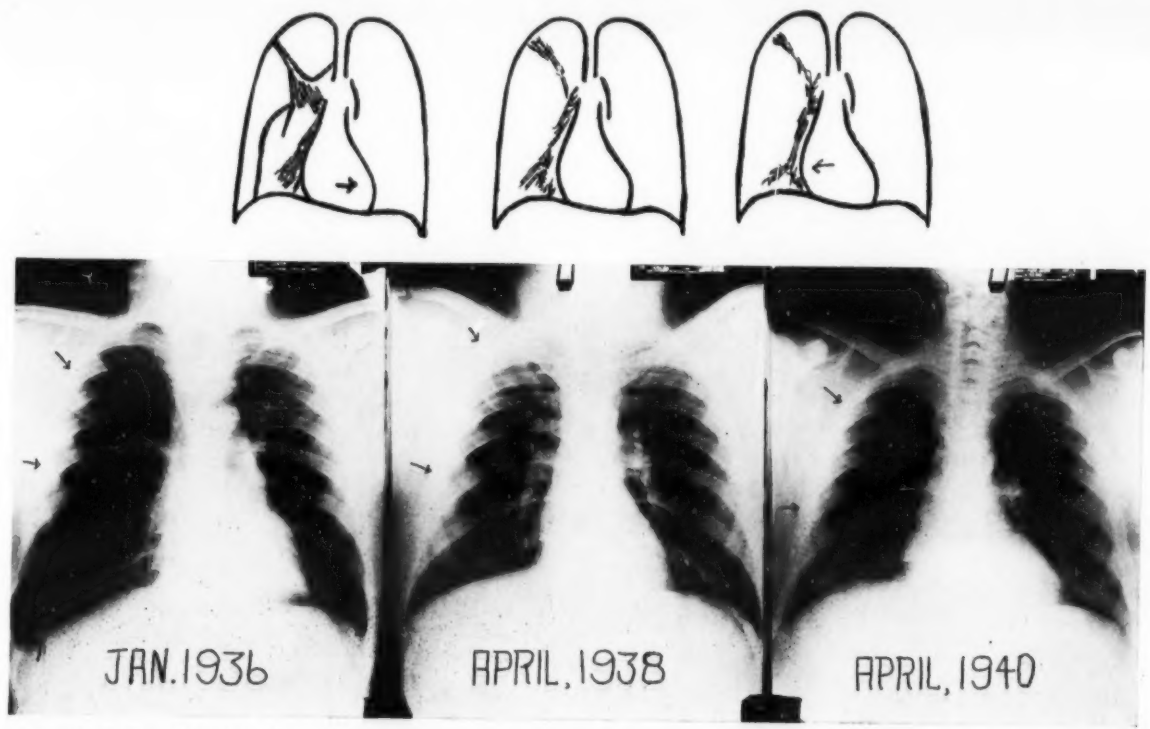


FIG. 1. F. B. #K41380. 20 year old white male, onset in July, 1932. Cough, loss of weight, malaise, slight expectoration. Caseo-cavernous lesion, right upper lung on X-ray film. Sputum positive for tubercle bacilli. Therapeutic pneumothorax commenced at once. Collapse effective, with early sputum conversion, despite a broad adhesion in 2nd interspace. Became ambulatory in 1933, and commenced full time work as a bartender in 1935. Pneumothorax was abandoned in 1938, and lung reexpanded uneventfully. Only residual was slight fibrosis in right second interspace, which was hardly visible on last checkup in 1940, even allowing for differences in technic.

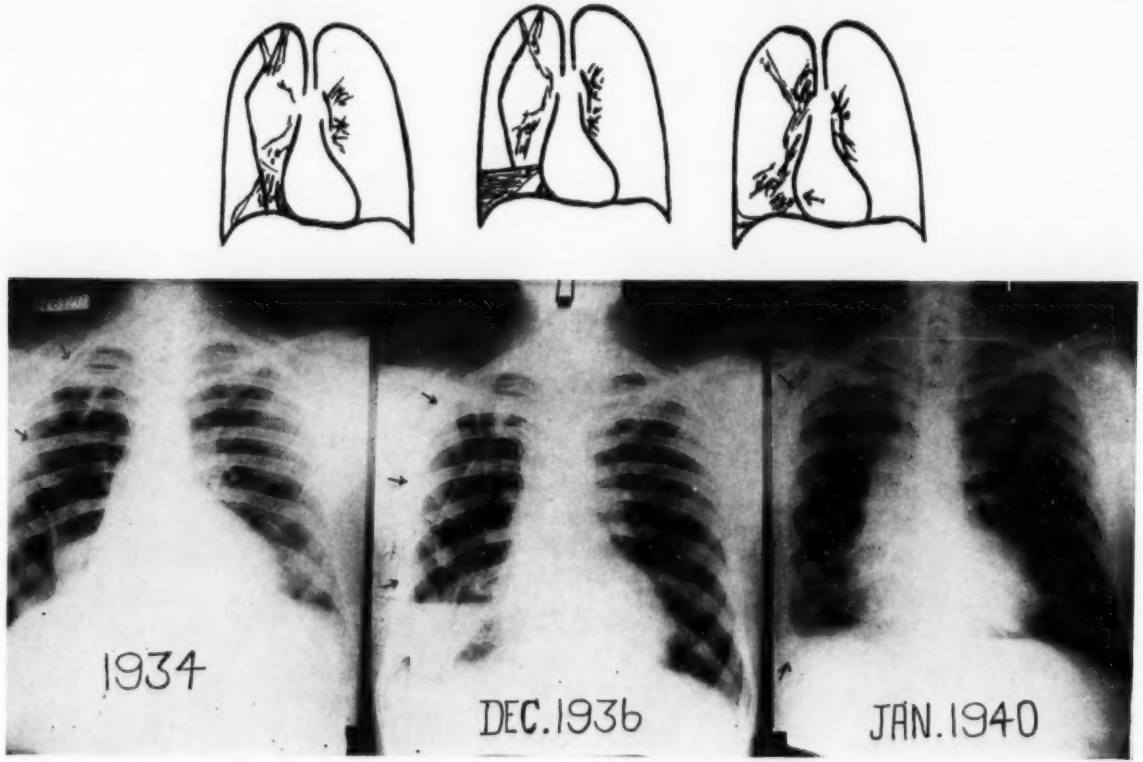


FIG. 2. N. K. #192030. 26 year old white male with onset in 1932. Extensive caseo-cavernous lesion of right upper lung. Therapeutic pneumothorax commenced at once, sputum being positive for tubercle bacilli. Sputum conversion and marked clinical improvement in several months, despite several dense apical adhesions. Developed a small amount of fluid in 1936, requiring aspiration. Lung was reexpanded uneventfully in 1938. Rather marked residual fibrosis, pleural thickening and mediastinal dislocation. No evidence of activity on clinical and X-ray checkup in 1940, and patient working full time as a steel worker.

thickening and mediastinal dislocation. No evidence of activity on clinical and X-ray checkup in 1940, and patient working full time as a steel worker.

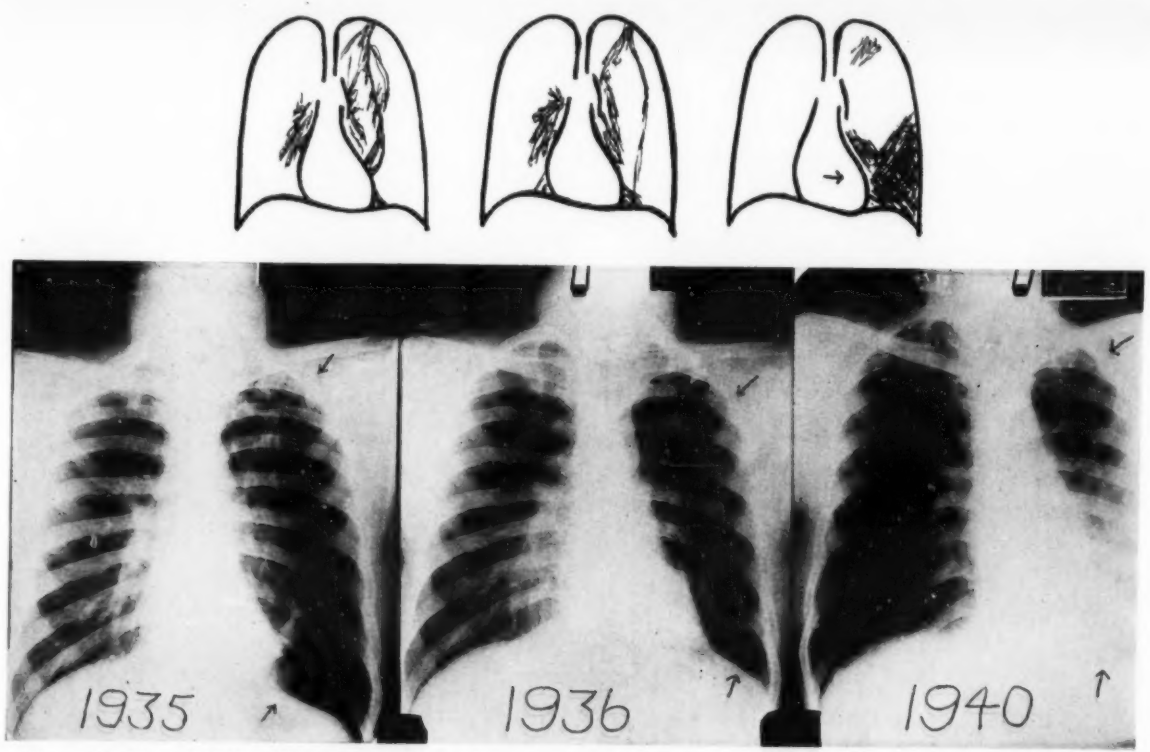


FIG. 3. S. K. #191569. 24 year old white male with onset in 1934. Soft infiltration of left upper lobe. Positive sputum. Artificial pneumothorax commenced with sputum conversion in a few months. Was transferred to ambulatory clinic in same year (1934) and received 600 cc. every two weeks. Worked part-time, and gradually gained weight. Reexpansion was begun in 1939, and some fluid accumulated. Residual fibrosis, obliteration of left costophrenic space, and slight dislocation of contents of mediastinal space.

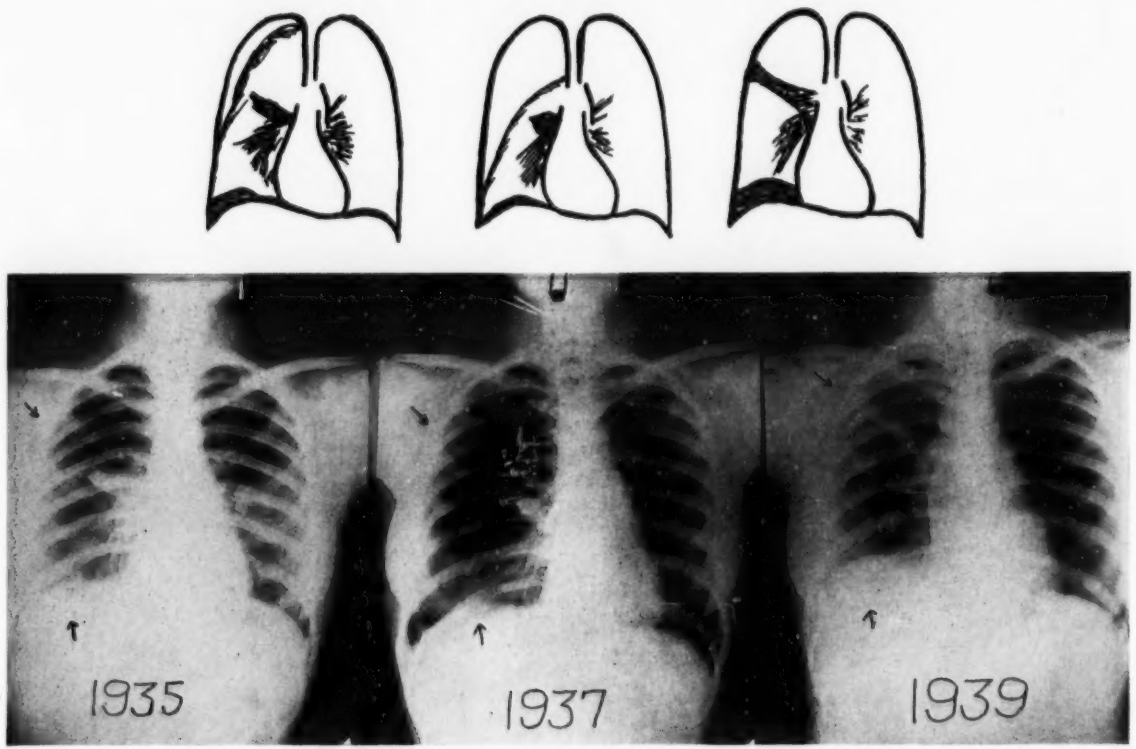


FIG. 4. D. B. #135586. 20 year old white female with onset in 1934. Loss of weight, malaise, cough, expectoration, and positive sputum. Soft infiltration of right upper lobe with small cavity formation. Artificial pneumothorax started at once, with immediate improvement. Received 500 cc. every two weeks. Sputum conversion in three months. Transferred to ambulatory clinic, and progress was satisfactory. Had a therapeutic abortion in 1938. Commenced reexpansion in 1939. Clinically well on last checkup in 1940.

ambulatory clinic, and progress was satisfactory. Had a therapeutic abortion in 1938. Commenced reexpansion in 1939. Clinically well on last checkup in 1940.

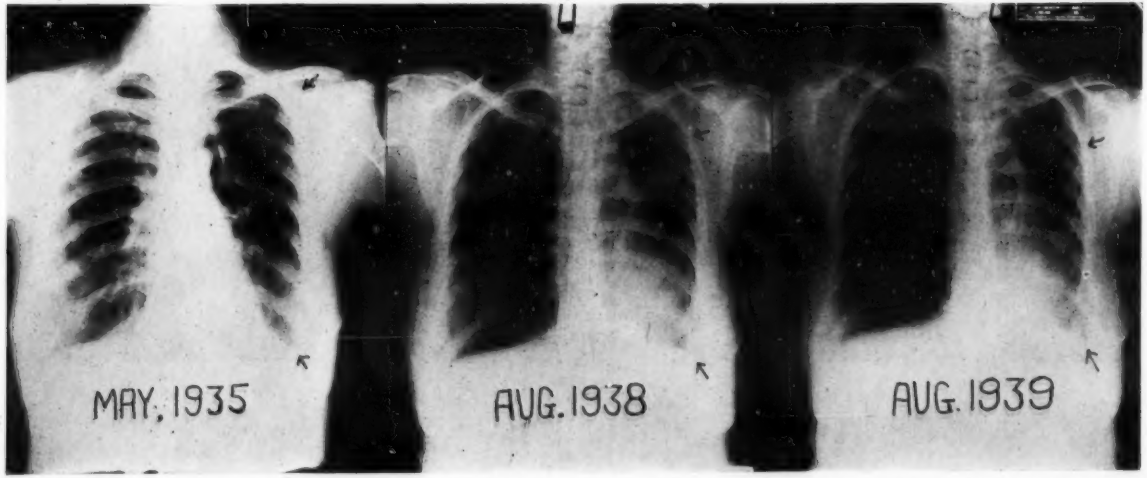


FIG. 5. M. H. #38320. White female, age 22 when pulmonary tuberculosis involving left upper lobe was discovered. Sputum positive for tubercle bacilli. Failed to improve on rest in sanatorium and therapeutic pneumothorax was commenced on left in 1934. Received 500 cc. every two weeks, transferring to ambulatory clinic in 1935. Lung was reexpanded uneventfully in 1937. Residual fibrosis, thickened pleura and slight mediastinal dislocation. Clinically well on last checkup in 1940.

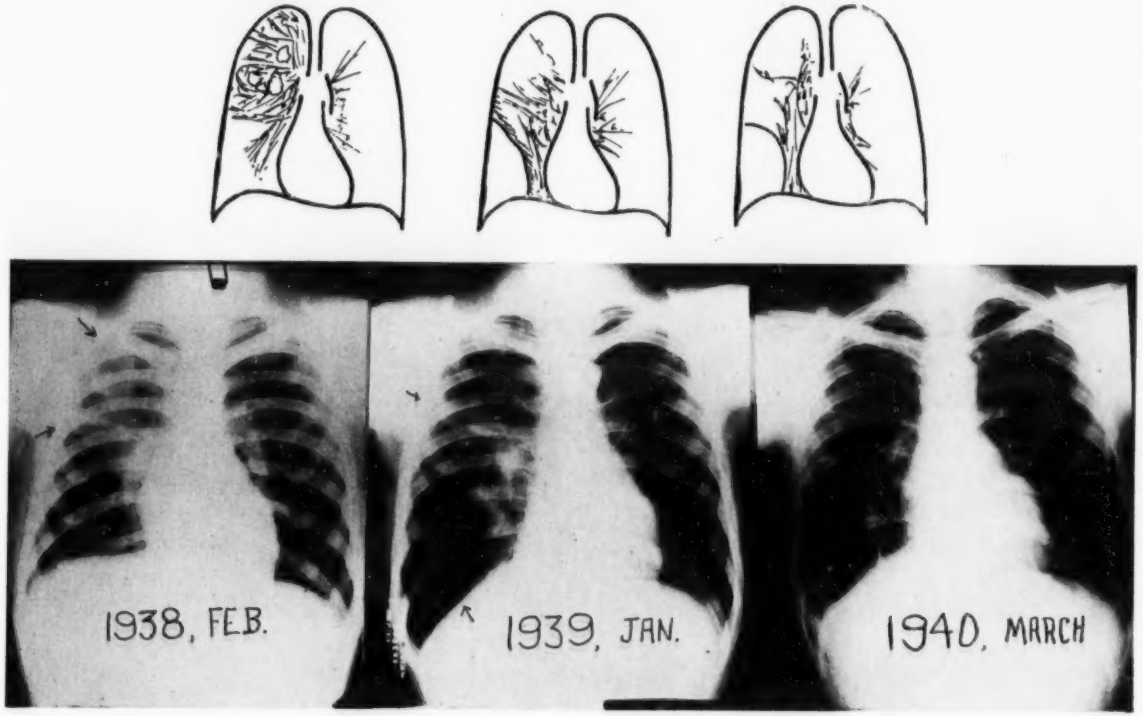


FIG. 6. J. W. (Pneumothorax Clinic (Broadway), Baltimore City Health Department). 20 year old white male, onset February, 1938, with cough, right chest pain, loss of weight, blood-streaked sputum. Sputum positive for tubercle bacilli, moderately advanced exudative lesion upper right lung. Therapeutic pneumothorax begun in March, 1938, receiving 400 cc. every week, later every two weeks. Pneumothorax pocket mostly at right base, but effective. Sputum conversion in 3 months, reexpansion commenced in 2 years. Reexpanded lung appears fibrosed and lesions inactive. He is now clinically well (1941).

3 months, reexpansion commenced in 2 years. Reexpanded lung appears fibrosed and lesions inactive. He is now clinically well (1941).

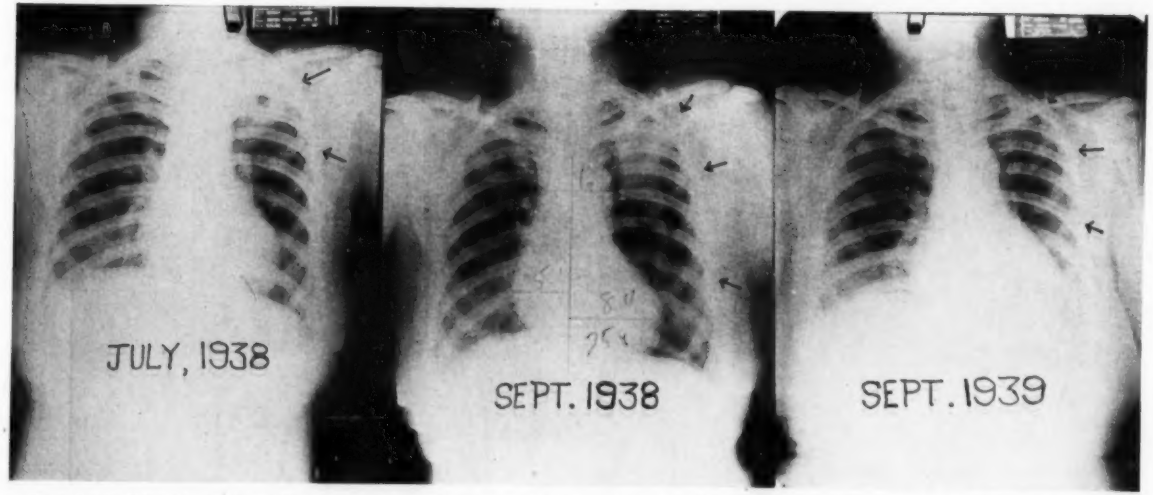


FIG. 7. B. W. #131920. 52 year old colored female. Diabetes Mellitus discovered in 1938 and routine chest film revealed caseo-cavernous lesion, left upper lobe. Sputum positive for tubercle bacilli. Therapeutic pneumothorax complicated by dense apical adhesions. Received 300 cc. every two weeks. Collapse therapy abandoned after 9 months. Reexpanded lung showed residual fibrosis, disappearance of cavity and slight thickening of pleura. Sputum persistently negative for tubercle bacilli on smears and cultures. Diabetes mild and well-controlled. On last checkup in 1940 she was clinically well.

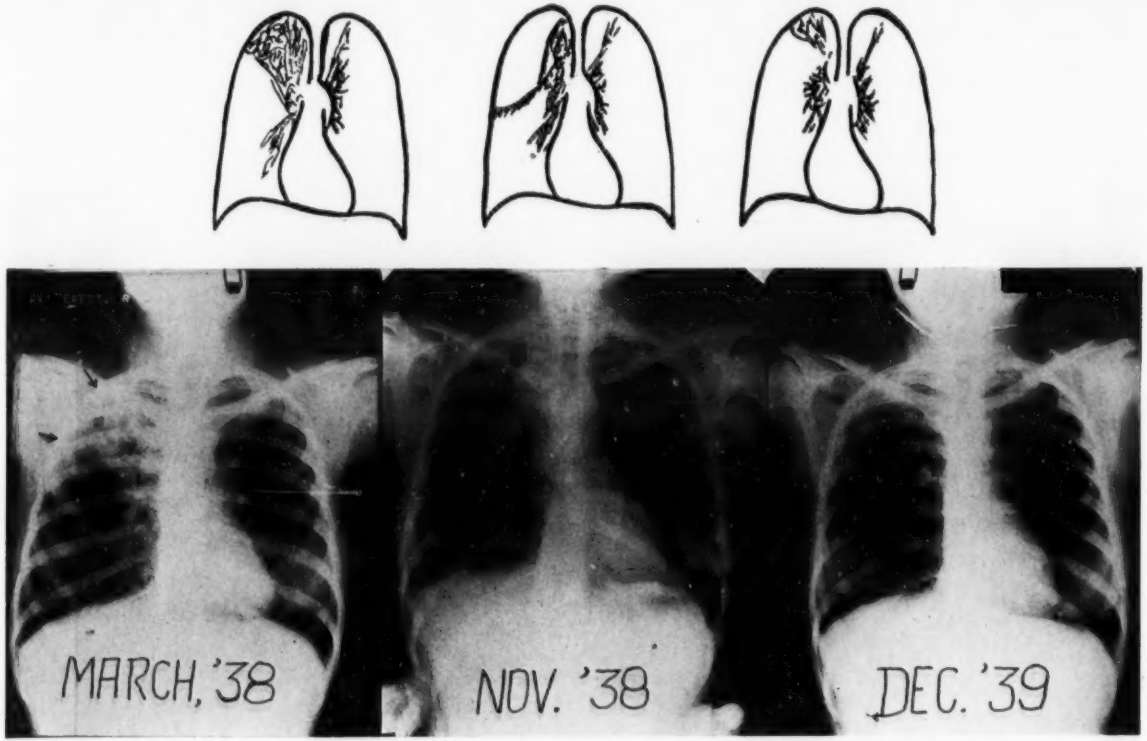
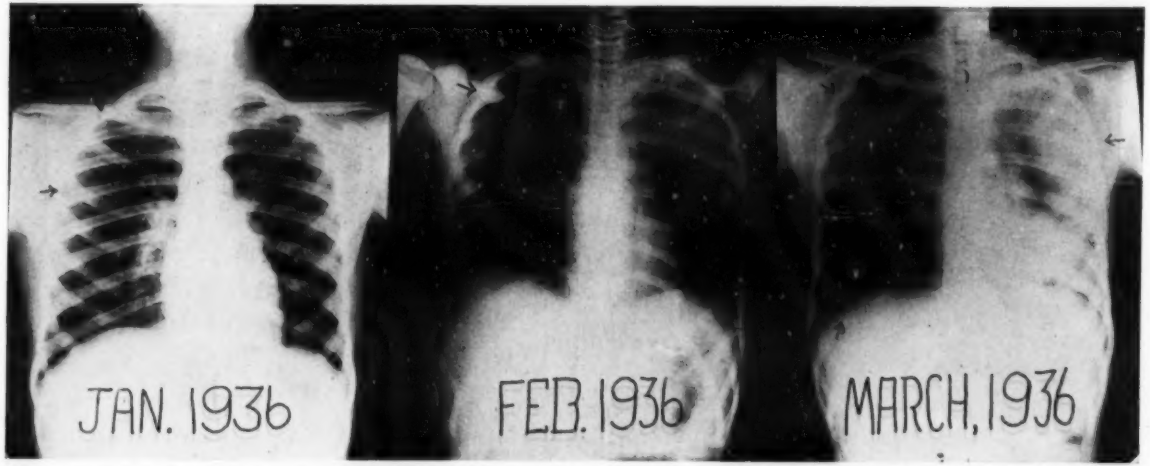


FIG. 8. T. G. #57853. 23 year old white female with onset in 1938. Soft infiltration with cavitation, right upper lobe, with positive sputum. Very marked constitutional reaction with fever, cough, streaking, loss of weight and strength. After stabilizing, artificial pneumothorax was commenced on right. Lower part of lung adherent, but apical pocket was effective. Rapid improvement clinically, conversion of sputum and X-ray improvement. In one year small space obliterated. Re-expanded lung showed much less parenchymal involvement, but complete healing was not apparent and strict rest was continued.

Rapid improvement clinically, conversion of sputum and X-ray improvement. In one year small space obliterated. Re-expanded lung showed much less parenchymal involvement, but complete healing was not apparent and strict rest was continued.



FIGS. 9–10. W. S. #122175. A colored male who at age one year was found to have a positive tuberculin test at the Harriet Lane Home. In 1936 he developed a cervical adenitis, and was found to have a soft infiltration of the right upper lobe, with a positive sputum. Artificial pneumothorax was induced on the right in February, 1936, with almost immediate spread to left upper lung. The patient was sent to a sanatorium, but he did not cooperate and did not rest as advised. Right lung was slowly reexpanded, and pneumothorax was commenced on the left, in August 1936. The patient left the sanatorium against advice and was followed in the ambulatory clinic. Right lung reexpanded, and by Oct. 1937 the lesion had apparently spread, and sputum was positive. The patient was then out of contact until 1940, when he returned. Left lung had reexpanded, with density of left base, but with retrogression of right upper lobe lesion. General condition was poor, and prognosis grave.

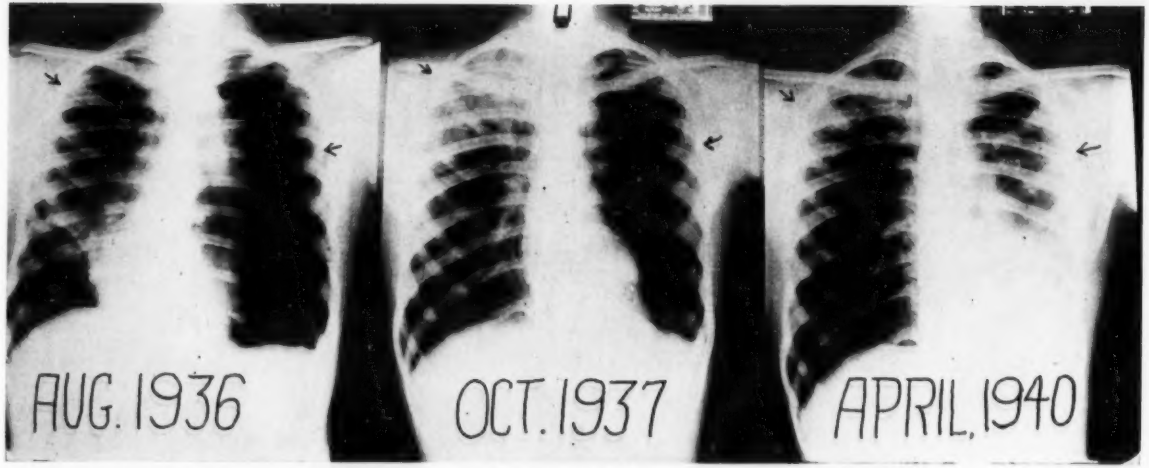
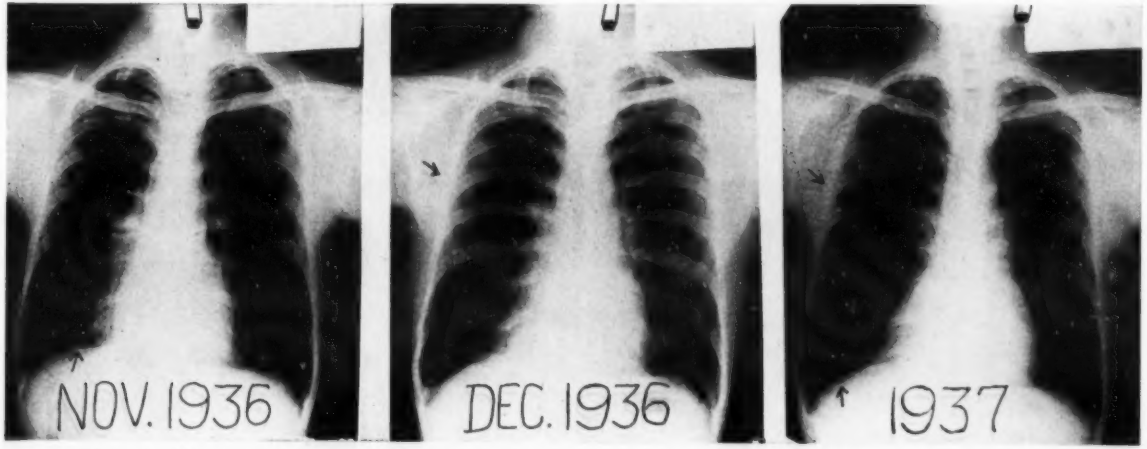


FIG. 10.

FIG. 10.



FIGS. 11–13. J. W. A 29 year old white male. Right lower lobe pulmonary tuberculosis in 1936, with pneumothorax therapy. Developed small amount of fluid in 1937, but sputum persistently negative by smear, culture and animal inoculation until 1938. Persistent positive culture in 1938 resulted in a bronchoscopy and a tuberculous lesion of the right lower lobe bronchus was found. This was cauterized over a long period with great improvement. Because of tendency of right lung to reexpand very rapidly, and persistence of pleural effusion, an oleothorax was established. Sputum was negative, and there was no sign of clinical activity on last check up in April, 1940. The patient has been gainfully employed for the past year.

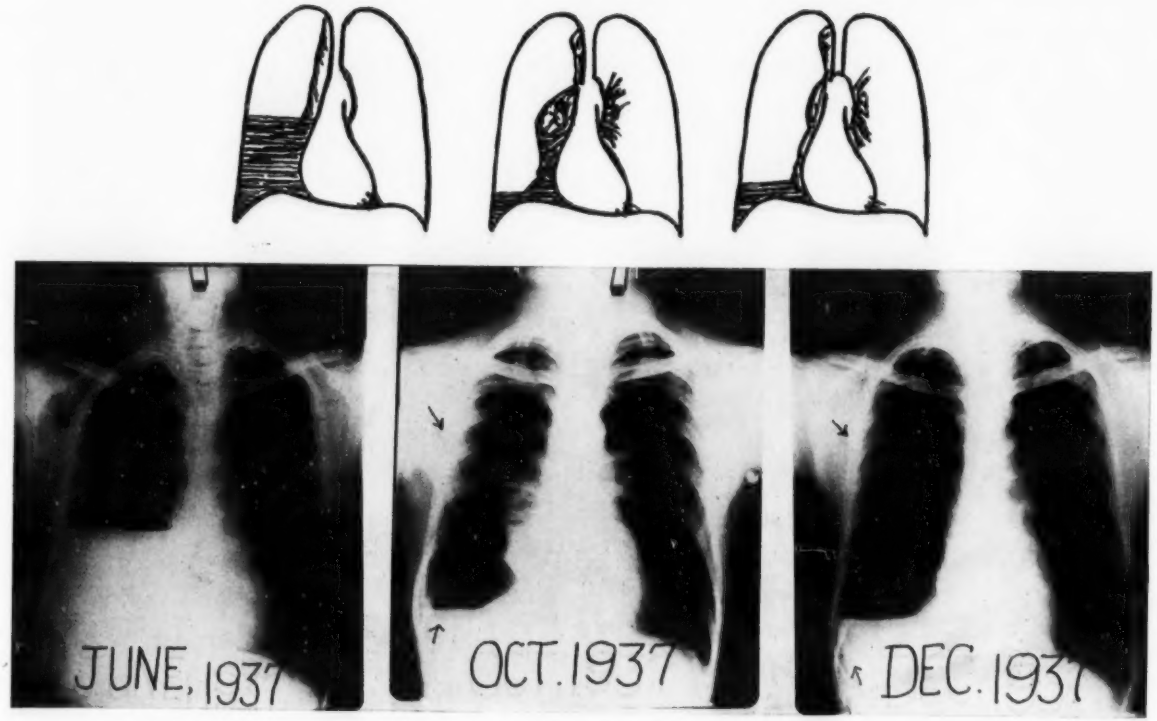


FIG. 12.

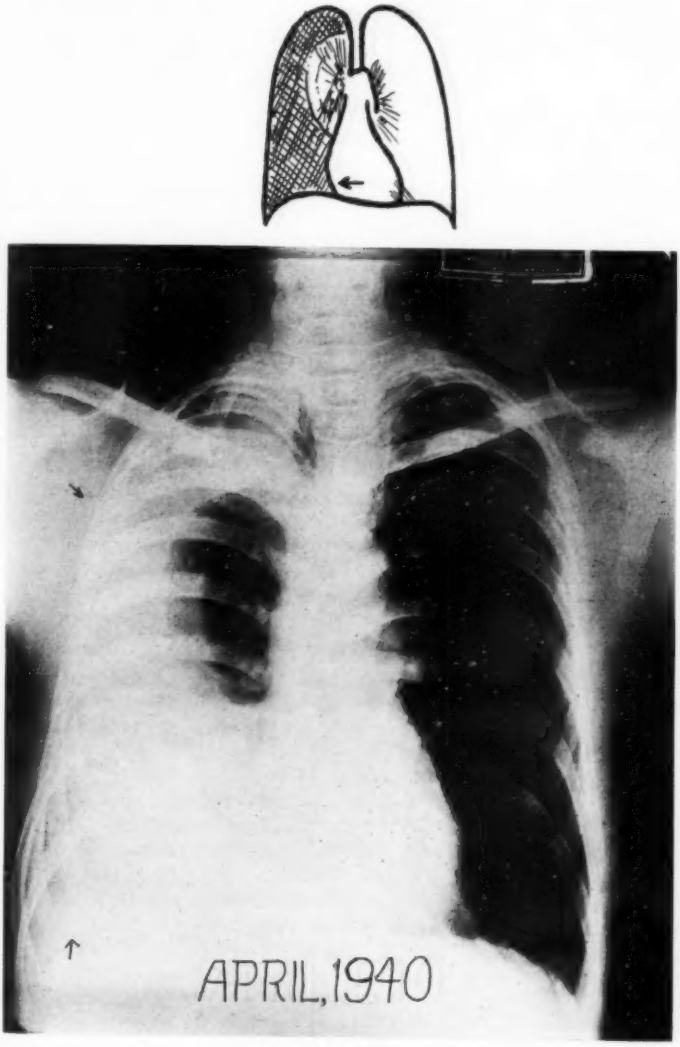


FIG. 13.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Textbook of Pathology. By WILLIAM G. MACCALLUM. 7th Ed., 1302 pp. Illus. $10.00. *W. B. Saunders Company, Philadelphia and London, 1940.*

For a quarter of a century Dr. MacCallum's book has been an inspiration to generations of students and a classic of medical literature. With each new edition admiration increases for the lucid and charming style of the book. In this, the Seventh Edition, the whole text has been revised in the light of advances in the medical sciences which have been so great during the past few years. There are excellent new illustrations, and the references to recent literature which have been added, direct the student, as in previous editions, to comprehensive papers with more complete bibliography.

S. S. B.

Manual of Allergy. By MILTON B. COHEN. 156 pp. $2.00. *Paul B. Hoeber, New York & London, 1941.*

This volume is intended to be a didactic handbook on allergy for the specific use of the general practitioner. Actually, the book is no more than an introduction to allergy and, therefore, will be of little practical value to the general practitioner. Many experienced internists and allergists will disagree with much that the author has written. There is too much stress on information that can be obtained from x-ray and fluoroscopic examinations. Too much space, for a book of this nature, is devoted to the studies of T. W. Todd, which, though interesting, are at times far-fetched. The technique of treating the hypersensitive individual with horse serum is to be deprecated. There are good features. The book is well organized and the contents are presented in a readable style.

E. L. K.

Pioneers in Acute Abdominal Surgery. By ZACHARY COPE. 135 pp. Illus. $2.50. *Oxford University Press, London: Humphrey Milford, 1939 (Oxford Medical Publications).*

This relatively short monograph describes in chronological sequence the history of the operative attack on acute diseases of the abdomen. Of the three bodily cavities, that which is the most difficult of approach was the first to be opened by the surgeon—clearly shown by the trephine holes in skulls from remote times. The thoracic cavity was frequently opened in early historic times for the condition of peri-pneumony (empyema); while the abdominal cavity was the last to be explored by the surgeon.

The author, classing the main abdominal crises as (1) obstruction of the alimentary canal, (2) inflammations of the viscera and peritoneum (due to visceral perforation), and (3) severe intraperitoneal bleeding, states that until the middle of the 19th century surgery had touched only the first group, and he, therefore, begins his book with a discussion of the obstructive group.

There follows a description of the treatment of strangulated inguinal hernia from the time of Celsus, through the next 1500 years during which time little advance in surgical methods was made, until Pierre Franco in 1556 told of his technique in cutting down on a glass rod inserted through an incision in the upper part of the scrotum.

The problem of resection of the bowel was brought into prominence by the valuable experimental work of Travers (1783–1858), by the intestinal suture of Lembert, and by the enterotome of Dupuytren devised to crush the spur of an artificial anus.

There follows a chapter on obstruction of the colon due to stricture, and its relief by colostomy, first done by Pillore of Rouen in 1776. No authentic record of operation for volvulus appeared before the introduction of anesthesia, the first case being that of Lindstredt and Waldenstrom in Sweden in 1878. Operations for intussusception were undertaken at an earlier date but none on the infant until 1863, well after the introduction of anesthesia. John Hilton in 1847, just before anesthetics were used, relieved an internal strangulation of the small bowel by incising a constricting band.

The second type of acute abdominal crisis, that caused by inflammation, is discussed in a chapter about the treatment of perforative peritonitis, beginning with the paper of Reginald Fitz, who in 1886 invented the term appendicitis, and recommended removal of the appendix. Willard Parker had, in 1867, published an article recommending an operation for opening perityphlitis abscess at an early state.

The story of surgical advance in the treatment of perforations of the stomach and intestines runs parallel to that of perforative appendicitis, but somewhat behind it. In 1883 Kocher saved the life of a patient shot through the stomach by suturing the perforation. Mickulicz, in 1884, closed a perforated peptic ulcer, but the first successful case was that of Heusner of Barmen in 1892.

Last in the book is the chapter dealing with severe intra-abdominal bleeding. J. S. Parry of Philadelphia first suggested laparotomy, ligation of the bleeding vessel, and removing the sac in women suffering from a ruptured extra-uterine pregnancy. Hallwright, a general practitioner of Birmingham, made the bold suggestion to Lawson Tait in 1881 of opening the abdomen and removing the ruptured fallopian tube in a patient on whom they were consulting. Tait refused and the patient died; but finally, in 1884, he performed the first successful operation for this condition.

I. R. T.

Gastric and Duodenal Ulcers. By HAROLD AVERY. 110 pp. 7/6d. *John Bale and Staples, London, 1940.*

This delightfully simple little monograph on peptic ulcers is so clearly and concisely written that it should prove readable to the layman—in particular, the ulcer patient—as well as the general practitioner for whom it is intended. The ten short chapters take up in order the anatomy, histology, physiology, pathology, etiology, clinical history, clinical examination, diagnosis, treatment, and complications of ulcers. The text is supplemented with numerous drawings and photographs which serve to clarify the written matter. To be sure, the drawings are highly diagrammatic and none too accurate from the standpoint of anatomical topography (for example, the sketch illustrating the blood supply of the stomach). Such shortcomings are excusable on the grounds that the author has sacrificed anatomical accuracy for the sake of simplicity and clarity. After all, he is not attempting to instruct surgeons in the art of gastric surgery.

Dr. Avery is particularly interested in the role of neurogenic factors in the etiology of ulcers. He presents an interesting discussion of "ulcer types" and lays considerable emphasis on emotional stress and strain as a factor in the causation or exacerbation of ulcer symptoms. He wisely points out the importance of treating the patient as a whole and not merely his ulcer. In the medical treatment of ulcers the author favors a modified Sippy regime with the liberal use of alkaline medication over a prolonged period. Complete dietary instructions are listed in the text. Dr. Avery hesitates to recommend the more radical Meulengracht regime of a full puree diet from the start, although he is impressed by the excellent results claimed for this treatment in cases of severe hematemesis. Aluminum hydroxide therapy, which has largely replaced the time-honored alkaline remedies of the past in many gastro-intestinal clinics, is mentioned briefly but does not receive the enthusiastic support which greeted its introduction in this country. It is conceivable that the author has not given this form of medication sufficient trial to justify final conclusions. The indications for surgical intervention are adequately epitomized under six headings.

To the reviewer it is most refreshing to find a discussion of gastric and duodenal ulcers so matter-of-fact, so full of common sense, and so devoid of the fantastic theories and complicated therapeutic procedures which characterize so much of the gastro-enterological literature. This book is heartily recommended, not only to the general practitioner for its practical advice, but also to the specialist in gastroenterology.

W. H. B.

Physical Medicine. By FRANK H. KRUSEN. 846 pp. Illus. $10.00. *W. B. Saunders Company, Philadelphia and London, 1941.*

This single volume textbook and reference book should be of great value to medical student and practicing physician alike. Their instruction in physical

therapy has been lamentably meagre and there has been need for the information so well assembled and recorded here. In this field of medicine we are particularly fortunate in having available a conservative and scholarly work by an experienced and outstanding authority.

As the author states in the preface, each physical agent is considered, as far as possible, under the following headings: (1) Introduction—definition—development—present status; (2) Physics; (3) Source, device or method of production; (4) Physiologic effects; (5) Technic of application; (6) Indications; (7) Contraindications, dangers and limitations; (8) Conclusions.

The book is divided into nine parts and twenty-two chapters in which are considered in detail thermotherapy, light therapy, electrotherapy, hydrotherapy and mechanotherapy, including massage, exercise and mechanical devices.

Part VII is devoted to the clinical aspects of physical therapy including chapters on its relation to general medicine and surgery, on the physical therapy of arthritis, on the relation of physical therapy to orthopedic surgery and on its relation to the management of backache.

Perhaps the present status of the subject justifies the inclusion in this volume of the last two chapters, namely, The Teaching of Physical Medicine and The Hospital Department of Physical Therapy.

If there is any lack of balance in the presentation it may be in the extent to which fever therapy and light therapy have been treated. These are subjects in which the author has been particulaly interested. It is not implied, however, that other sections of the book have in any way been neglected.

A bibliography, in some cases quite extensive, is supplied at the end of each part. The illustrations are numerous and quite good.

T. P. S.

Neoplastic Diseases. A Treatise on Tumors. By JAMES EWING. 4th ed. 1160 pp. Illus. $14.00. *W. B. Saunders Company, Philadelphia and London, 1940.*

The appearance of a new edition of this standard and comprehensive work is a welcome event. The author has added over 40 new figures since the last edition. The detail of the photomicrographs is excellent. The text has gained especially by the inclusion of new material on ovarian tumors. The text, however, suffers by references to "recent" literature of 1909 and 1913 on subjects that might well be omitted. Unfortunately the price of this volume places it out of reach of many, especially the average medical student.

R. H. F., JR.

Clinical Nursing in Medicine. By JULIUS JENSEN and DEBORAH MACLURG JENSEN. 808 pp. Illus. $3.25. *The Macmillan Company, New York, 1941.*

When the authors wrote this book with the hope in mind of devising a readable, up-to-date text on elementary medicine which was to serve the nurse doubly as a

text and as a reference book, the purpose was fulfilled very thoroughly and in a manner which is a departure from the usual textbook of medical nursing.

The development of Medicine as a science, history taking, diagnostic methods and statistics are covered in the introduction. The following units deal with infection and immunity, metabolic and deficiency diseases, infectious diseases, allergy, and diseases of the respiratory, cardio-vascular, blood forming, gastro-intestinal, urinary, endocrine and nervous systems.

Each unit is quite complete in itself with excellent illustrations by charts, pictures, and graphs which always arouse much interest on the part of the student. Each unit has an extensive list of references to the various fields from which the material has been drawn.

At the conclusion of the book is a dietary index contributed by Doctors Rusk, Newman and Kenamore. This includes many of the menus useful in treating medical diseases, with emphasis on vitamin and mineral content.

This book provides one of the most complete studies on clinical medical nursing thus far available and should be welcomed as affording clear, concise, up-to-date information on its subject.

Both of the authors have been in the field of education and are well versed in medical science: Dr. Julius Jensen as Assistant Professor of Medicine, and Mrs. Deborah Maclurg Jensen as Lecturer in Nursing Education, Washington University, St. Louis, Mo.

M. S.

Orbital Tumors. Results Following the Transcranial Operative Attack. By WALTER E. DANDY. 168 pp. Illus. $5.00. *Oskar Piest, New York, 1941.*

In this monograph Dr. Dandy has described thirty-four cases of orbital tumors of which twenty-four were treated surgically. The book is an invaluable contribution on the surgical treatment of orbital tumors and it marks another milestone in our knowledge on this aspect of a difficult problem. The author has proven beyond question that in combined intracranial and intraorbital tumors the method of intracranial approach with removal of the roof of the orbit provides a more satisfactory exposure of the orbital tumor than can be obtained in any other manner.

The same type of operation is advised by the author in cases of purely orbital tumor. In the preface to the monograph Dr. Alan C. Woods wrote, "Since 1934, in the Johns Hopkins Hospital, it has been the custom for patients with orbital tumors to be operated only after consultation between the ophthalmological and neurological services. Tumors lying in the anterior portion of the orbit, when there is no reason to suspect an intracranial extension, are operated either by a conjunctival or upper orbital route. All tumors lying deep in the orbit, and invariably any tumor in which there is any reason to suspect an intracranial extension, are routinely referred from the ophthalmological to the neurosurgical service for operation. That this method of arbitrarily separating orbital tumors into two groups, one in the domain of the ophthalmic surgeon, and one in the domain of

the neurosurgeon, is thoroughly satisfactory and entirely justified, is fully substantiated by this monograph of Dr. Dandy". This reviewer is in full accord with Dr. Woods' statement, and would further point out that Dr. Dandy's monograph includes only such cases of deep orbital tumors and no cases (unless possibly case 1) in which non-surgical therapy could have been adequate.

The monograph contains 100 illustrations. The operative sketches, of which there are many, are beautiful and all the illustrations are good. The printing is excellent.

F. B. W.

Studies on Tuberculosis. American Journal of Hygiene Monographic Series, No. 16, February 1941. 198 pp. Illus. $1.10. *The Johns Hopkins Press, Baltimore, 1941.*

These studies comprise a series of four excellent papers. The first two, by E. J. Saward, P. Putnam and E. Opie, deal with "The Spread of Tuberculosis in Negro Families in Jamaica", and with "The Fate of Negro Persons of a Tropical Country, Jamaica, B. W. I., after Contact with Tuberculosis". The latter two report "A Survey of Tuberculous Infection in a Rural Area of East Alabama", and "The Fate of Persons Exposed to Tuberculosis in White and Negro Families in a Rural Area of East Alabama", studies carried out by A. H. Graham, P. W. Auston and P. Putnam.

The primary purpose of the studies, conducted with the aid of grants from the International Health Division of the Rockefeller Foundation, was to determine the similarities and the differences in the morbidity, mortality, character and extent of tuberculosis in the negro and in the white as it occurs in temperate and in tropical environments; and also the influence of exposure, familial and extrafamilial, upon them.

The statistical and biometric analyses on which these studies are based are presented clearly and convincingly. The volume will be read with profit by all interested in tuberculosis and in epidemiology.

C. R. A.

Physical Diagnosis. By RALPH H. MAJOR. 2nd ed. 464 pp. Illus. $5.00. *W. B. Saunders Company, Philadelphia and London, 1940.*

Although very little about physical diagnosis can ever be learned from the printed page, medical students entering upon the study of internal medicine should find the revised edition of Dr. Major's text an interesting and helpful guide. It is in no sense a reference book. The whole subject of physical diagnosis has been skillfully condensed into a relatively small volume, but condensation has inevitably led in certain instances to neglect of physiological implications of the physical signs. Since the students' grasp of the subject must ultimately depend upon an understanding of pathological physiology, the omission of these physiological

explanations in places seems unfortunate. One of the most praiseworthy features of the book is the abundance of photographs and diagrams illustrating the text. Although the illustrations in the main depict only far advanced disease and, therefore, may give the student a false impression as to the prevalence of medical monstrosities, they serve an important function by being sufficiently vivid to impress the mind of the reader.

W. B. W., Jr.

BOOKS RECEIVED FOR REVIEW

Brucellosis (Undulant Fever). By Harold J. Harris. 286 pp. Illus. $5.50. *Paul B. Hoeber, New York & London, 1941.*

Lectures on Conditioned Reflexes. By Ivan Petrocitch Pavlov. Vol. 2. Conditioned Reflexes and Psychiatry. Translated and edited by W. Horsley Gantt. 199 pp. Illus. $4.00. *International Publishers, New York, 1941.*

Histopatología del Cerebelo en la Parálisis General Progresiva. By Ramón Melgar. 110 pp. Illus. *Imprenta de Alfredo Frascoli, Buenos Aires, 1940.*

Tuberculosis y Psicopatías. By Ramón Melgar. 266 pp. Illus. *Talleres Gráficos "Gasperini," Buenos Aires, 1937.*

Pinel. Monografía para el Seminario de la Cátedra de Historia de la Medicina. By Ramón Melgar. 64 pp. *Buenos Aires, 1940.*

Lachish II. The Fosse Temple. By Wellcome-Marston Archaeological Research Expedition to the Near East. 104 pp. 73 pl. $8.50. *Oxford University Press, New York [etc.], 1940.*

Clinical Aspects of the Electrocardiogram. By Harold E. B. Pardee. 4th ed. 434 pp. Illus. $5.75. *Paul B. Hoeber, New York and London, 1941.*

Textbook of Ophthalmology. By Sanford R. Gifford. 2nd ed. 470 pp. Illus. $4.00. *W. B. Saunders Company, Philadelphia and London, 1941.*

Essentials of Gynecology. By Leo Brady and Ethna Louise Kurtz. 257 pp. Illus. $2.75. *The Macmillan Company, New York, 1941.*

Clinical Nursing in Medicine. By Julius Jensen and Deborah Maclurg Jensen. 808 pp. Illus. $3.25. *The Macmillan Company, New York, 1941.*

Synopsis of Diseases of the Heart and Arteries. By George R. Herrmann. 2nd ed. 468 pp. Illus. $5.00. *C. V. Mosby Company, St. Louis, 1941.*

Primer for Diabetic Patients. By Russell M. Wilder. 7th ed. 184 pp. Illus. $1.75. *W. B. Saunders Co., Philadelphia and London, 1941.*

Orbital Tumors. By Walter E. Dandy. 168 pp. Illus. $5.00. *Oskar Piest, New York, 1941.*

Science and Seizures. By William G. Lennox. 258 pp. Illus. $2.00. *Harper & Brothers, New York and London, 1941.*

American Illustrated Medical Dictionary. By W. A. Newman Dorland. 19th ed. 1647 pp. Illus. $7.00. Thumb-Indexed, $7.50. *W. B. Saunders Company, Philadelphia and London, 1941.*

Infantile Paralysis. By PHILIP LEWIN. 372 pp. Illus. $6.00. *W. B. Saunders Company, Philadelphia and London, 1941.*

X-ray Therapy of Chronic Arthritis. By KARL GOLDHAMER. 131 pp. Illus. $2.00. *Radiologic Review Publishing Co., Quincy, Illinois, 1941.*

Effective Living. By C. E. TURNER and ELIZABETH MCHOSE. 432 pp. Illus. $1.90. *C. V. Mosby Company, St. Louis, 1941.*